

EXAMINING THE REGULATION OF DIAGNOSTIC TESTS AND LABORATORY OPERATIONS

HEARING BEFORE THE SUBCOMMITTEE ON HEALTH OF THE COMMITTEE ON ENERGY AND COMMERCE HOUSE OF REPRESENTATIVES ONE HUNDRED FOURTEENTH CONGRESS FIRST SESSION

NOVEMBER 17, 2015

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¹Dr. Shuren did not answer submitted questions for the record by the time of printing.

²The discussion draft has been retained in committee files and also is available at http://docs.house.gov/meetings/IF/IF14/20151117/104127/BILLS-114pih-HR_____.pdf.

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EXAMINING THE REGULATION OF DIAGNOSTIC TESTS AND LABORATORY OPERATIONS

TUESDAY, NOVEMBER 17, 2015

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:03 a.m., in room 2322, Rayburn House Office Building, Hon. Joseph R. Pitts (chairman of the subcommittee) presiding.

Members present: Representatives Pitts, Guthrie, Barton, Shimkus, Murphy, Burgess, Blackburn, Lance, Griffith, Bilirakis, Long, Ellmers, Bucshon, Brooks, Collins, Green, Capps, Butterfield, Castor, Schrader, Kennedy, Cárdenas, and Pallone (ex officio).

Staff present: Rebecca Card, Assistant Press Secretary; Carly McWilliams, Professional Staff Member, Health; Graham Pittman, Legislative Clerk; Heidi Stirrup, Health Policy Coordinator; John Stone, Counsel, Health; Christine Brennan, Democratic Press Secretary; Jeff Carroll, Democratic Staff Director; Tiffany Guarascio, Democratic Deputy Staff Director and Chief Health Advisor; Samantha Satchell, Democratic Policy Analyst; and Kimberlee Trzeciak, Democratic Health Policy Advisor.

Mr. PITTS. The subcommittee will come to order. The Chair will recognize himself for an opening statement.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Throughout the 21st Century Cures initiative, biomarkers, precision medicine, and targeted therapies were a few of the most consistently uttered terms and concepts. In order to advance each of them, we must establish a regulatory environment that fosters the development of, and access to, innovative, accurate, and reliable diagnostic testing. Such tests are increasingly important not only in diagnosing the onset of a specific disease or condition, but in determining the right course of treatment or procedure.

It goes without saying that tests providing information to a doctor or consumer are fundamentally different products than traditional medical devices, which actually deliver therapy to, or are implanted in, a patient. Nonetheless, while FDA has used its medical device authorities to review and oversee tests developed by outside

entities that are then sold to laboratories, the agency has not actively regulated laboratory-developed tests, or LDTs.

Last year, a week after we held a roundtable downstairs that highlighted the importance of this very topic, FDA announced that it would no longer exercise such enforcement discretion and detailed how the agency proposes to apply its medical device authorities to LDTs.

Today, I am far less interested in litigating the boundaries of current FDA or CMS legal authority, but in hearing from our witnesses how such authority could be clarified or improved, understanding the unique and evolving nature of what is being regulated and each agency's area of expertise.

In response to a white paper the committee circulated at the end of last year asking these very questions, we heard from a number of labs and pathologists that FDA should only have a limited role, if any, in regulating a select set of tests as medical devices. The rest, in their opinion, should be overseen by CMS through an updated Clinical Laboratory Improvement Amendments program. This is despite the fact that CMS has stated that they do not have the resources, the expertise, or the willingness to take on what is being asked of them. I am eager to hear what Dr. Conway has to say on this matter.

We also received comments from a number of manufacturers, as well as over 40 patient groups, that FDA, not CMS, needs to be in the driver's seat, and that tests that have the same impact on a patient should be held to the same standards, regardless of who does the development. This is despite the fact that laboratories are uniquely nimble environments where pathologists continually modify and improve tests in ways that manufacturers cannot.

I am well aware that this has been at times a heated debate with passionate advocates on both sides. With such a backdrop, I want to particularly commend the manufacturers, the laboratories, and other healthcare institutions that have been willing to roll up their sleeves and find as much common ground as possible through constructive dialogue, a willingness to compromise, and a pragmatic understanding of what a viable, modern framework entails.

I do not believe that imposing a new regulatory reality on an increasingly important component of our healthcare system via guidance is the best way to address these issues. These products warrant a regulatory system designed with them in mind. They should not be shoehorned into a system that was drafted in the 1970s.

This committee has clearly shown that we are willing and able to move complicated, comprehensive, bipartisan legislation. The discussion draft the committee circulated, along with the hearing notice, is of course not perfect, but it is a serious document based on significant consensus, and I would ask that all of the stakeholders out there, including our two distinguished witnesses, help us improve it as the process continues.

With that, I would like to thank Dr. Shuren, a frequent, always welcome visitor, as well as Dr. Conway, for their willingness to testify today, and I look forward to working with them on these issues going forward.

[The discussion draft is available at <http://docs.house.gov/meetings/IF/IF14/20151117/104127/BILLS-114pih-HR-----.pdf>.]

[The prepared statement of Mr. Pitts follows:]

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

Throughout the 21st Century Cures initiative, “biomarkers,” “precision medicine,” and “targeted therapies” were a few of the most consistently uttered terms and concepts. In order to advance each of them, we must establish a regulatory environment that fosters the development of and access to innovative, accurate and reliable diagnostic testing.

Such tests are increasingly important, not only diagnosing the onset of a specific disease or condition, but in determining the right course of treatment or procedure. It goes without saying that tests providing information to a doctor or consumer are fundamentally different products than traditional medical devices which actually deliver therapy to or are implanted in a patient. Nonetheless, while FDA has used its medical device authorities to review and oversee tests developed by outside entities that are then sold to laboratories, the agency has not actively regulated laboratory developed tests, or LDTs.

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With that I would like to thank Dr. Shuren—a frequent and always welcome visitor—as well as Dr. Conway, for their willingness to testify today. I look forward to working with them on these issues going forward.

Mr. PITTS. And I now recognize the ranking member, Mr. Green, 5 minutes for his opening statement.

**OPENING STATEMENT OF HON. GENE GREEN, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. GREEN. Thank you, Mr. Chairman, and thank you for calling this hearing today, and I want to welcome our witnesses from the FDA and the CMS.

The role of diagnostic tests in our healthcare system has changed dramatically since Congress passed the medical device amendments in 1976 and added in vitro diagnostics to the device definition. It has been almost 4 decades, and the evolution of modern medicine and the advancement of science has surpassed what everyone could imagine at the time. The enthusiasm around precision medicine is high, and the potential of diagnostics to further transform the treatment of disease is limitless.

When the FDA first began regulating medical devices, applicable regulatory requirements for lab-developed tests, or LDTs, were not enforced because they were relatively simple tests, generally combined the local labs, and frequently used for rare conditions.

Today, LDTs have increased in complexity and availability. They are often used to diagnose serious medical conditions, and many have major impact on patient care. Not only have LDTs become sophisticated, the role that these tests play in delivery of health care has expanded.

The Centers for Disease Control and Prevention estimated that approximately 6.8 billion laboratory tests are administered each year. An analysis found that results from the clinical laboratory tests influence about 70 percent of healthcare decisions.

The clinical laboratory amendments of 1988 created minimum standards of quality for all clinical labs in the country. The Centers for Medicare and Medicaid Services, CMS, has jurisdiction over the program, and CLIA has successfully improved the quality of the clinical labs in accuracy of testing for nearly 25 years.

However, under CLIA CMS does not confirm the clinical validation of LDTs, meaning that they do not look as to whether it is a particular test accurately that identifies, measures, or predicts the absence or the presence of a clinical condition. These known gaps in oversight have been a source of concern to this committee and to the healthcare community at large.

Yesterday, the Food and Drug Administration released a report that included 20 case studies of problematic tests from labs that were following the minimum requirements of CLIA but proposed real risk to patients. In an area of so much promise and significance to patient care, the accuracy, reliability, and clinical meaningfulness of all diagnostic tests, regardless of where they are created, must be a top priority for healthcare providers, test developers, regulators, and lawmakers.

Last year, the FDA issued a draft regulatory framework to phase in enforcement regulatory requirements, including premarket review, adverse event reporting for LDTs that pose greater risk to patients if their results are not accurate and reliable. And I appreciate FDA's efforts to ensure that tests are supported by rigorous evidence and that patients and healthcare providers can have confidence in their results.

That said, I share the opinion of my colleagues that legislation is both appropriate and necessary to modernize clinical laboratory

diagnostic oversight. The legislative solution is surely the surest way to establish a framework that will be embraced by stakeholders, avoid litigation, extended uncertainty, and foster innovation of new clinical diagnostic tests.

The FDA's approach to this draft guidance let to a number of important questions, but the guidance documents also spurred a larger conversation about the overarching need to modernize oversight of these unique and increasingly important tests.

During the 21st Century Cures initiative, as part of the broad effort to close the gap between science of cures and how we regulate medical products, the committee hosted a roundtable on precision medicine and advances in diagnostic testing. The committee also released a white paper on diagnostic test regulation and received outpouring of feedback from stakeholders.

While all parties did not agree on all the principles, much less specifics, it was abundantly clear that any regulatory framework for diagnostic tests must prioritize patient benefit and allow for continued innovation and investment through regulatory certainty and appropriate regulatory controls.

There is urgent need to establish clear and logical lines separating the practice of medicine and the actual conduct of the diagnostic tests and the development and manufacturing of diagnostic tests so that the promise of 21st century medicine can be fully realized.

Today, we will hear from FDA and CMS about each agency's respective role in the oversight and regulation of clinical laboratory tests. Members of the committee will have questions about the appropriate role of each agency and any updated framework, and how Congress can best promote robust investment and innovation while protecting patient safety.

Mr. Chairman, I look forward to hearing from our witnesses, and I yield back.

[The prepared statement of Mr. Green follows:]

PREPARED STATEMENT OF HON. GENE GREEN

Good morning, and thank you all for being here today.

The role of diagnostic tests in our healthcare system has changed dramatically since Congress passed the Medical Device Amendments in 1976 and added in-vitro diagnostics to the device definition.

It has been almost four decades, and the evolution of modern medicine and advancement of science has surpassed what anyone could have imagined at that time.

The enthusiasm around precision medicine is high, and the potential of diagnostics to further transform the treatment of disease is limitless.

When FDA first began regulating medical devices, applicable regulatory requirements for lab-developed tests or "LDTs" were not enforced because they were relatively simple tests, generally confined to local labs, and frequently used for rare conditions.

Today, LDTs have increased in complexity and availability. They are often used to diagnose serious medical conditions, and many have a major impact on patient care.

Not only have LDTs become more sophisticated, the role these tests play in the delivery of health care has expanded.

The Centers for Disease Control and Prevention estimated that approximately 6.8 billion laboratory tests are administered each year.

Another analysis found that results from clinical laboratory tests influence around 70 percent of healthcare decisions.

The Clinical Laboratory Amendments of 1988 created minimum standards of quality for all clinical labs in the country.

The Centers for Medicare and Medicaid Services (CMS) has jurisdiction over the program, and CLIA has successfully improved the quality of clinical labs and accuracy of testing for nearly 25 years.

However, under CLIA, CMS does not confirm the clinical validity of LDTs, meaning they do not look at whether a particular test accurately identifies, measures, or predicts the absence or presence of a clinical condition.

These known gaps in oversight have been a source of concern to this committee, and to the healthcare community at large.

Yesterday, the Food and Drug Administration (FDA) released a report that included 20 case studies of problematic tests from labs that were following the minimum requirements of CLIA, but posed real risk to patients.

In an area so much promise and significance to patient care, the accuracy, reliability and clinical meaningfulness of all diagnostic tests—regardless of where they are created—must be a top priority of healthcare providers, test developers, regulators, and lawmakers.

Last year, the FDA issued a draft regulatory framework to phase in enforcement of regulatory requirements, including premarket review and adverse event reporting, for LDTs that pose greater risk to patients if their results are not accurate and reliable.

I appreciate the FDA's efforts to ensure that tests are supported by rigorous evidence, and that patients and healthcare providers can have confidence in their results.

That said, I share the opinion of my colleagues that legislation is both appropriate and necessary to modernize clinical laboratory diagnostics oversight.

A legislative solution is the surest way to establish a framework that will be embraced by stakeholders, avoid litigation and extended uncertainty, and foster innovation of new clinical diagnostic tests.

The FDA's approach in its draft guidance led to a number of important questions, but the guidance documents also spurred a larger conversation about the overarching need to modernize oversight of these unique and increasingly important tests.

During the 21st Century Cures Initiative, as part of the broad effort to close the gap between the science of cures and how we regulate medical products, the committee hosted a roundtable on precision medicine and advances in diagnostic testing.

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While all parties did not agree on all principles, much less specifics, it was abundantly clear that any regulatory framework for diagnostic tests must prioritize patient benefit, and allow for continued innovation and investment through regulatory certainty and appropriate regulatory controls.

There is an urgent need to establish clear and logical lines separating the practice of medicine, the actual conducting of a diagnostic test and the development and manufacturing of such tests, so that the promise of 21st century medicine can be fully realized.

Today, we will hear from FDA and CMS about each agency's respective role in the oversight and regulation of clinical laboratory testing.

Members of the committee will have questions about the appropriate role of each agency in any updated framework, and how Congress can best promote robust investment and innovation, while protecting patient safety.

I look forward to hearing from our witnesses and I yield back the balance of my time.

Mr. PITTS. The Chair thanks the gentleman, now recognizes Dr. Burgess in lieu of Chairman Upton, 5 minutes.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. Thank you, Mr. Chairman.

I appreciate the opportunity that we have before us with this hearing, but I do want to say at the outset, with everything else that is going on, this may be one of the most important and at the same time the most frightening concepts that is before the Congress right now. We are talking about a proposal that may not just

stifle but eliminate medical innovation, something which this country has excelled for decades, and we are also opening the door for the first Federal regulation of the practice of medicine, not the needles and IV solutions, the actual diagnostic thought processes that go in to practicing medicine.

Let me just say at the outset I do strongly believe in the potential of genomic medicine. I understand how important it is to really understand illness at a molecular level, quickly diagnose it, and get the treatment that is appropriate for the patient with a minimal amount of side effects.

A year and a half ago, when the President talked about precision medicine during his State of the Union Address, I thought that was a very positive development. There are not many places where the White House and I agree on anything, but here was some common ground, and I took it to heart.

Laboratory testing produces the informational building blocks that are at the heart of precision medicine. As former Administrator Mark McClellan at CMS said, we have got to get the right treatment at the right time to the right patient.

We are not talking about test kits that are put in a box and shipped across State lines but medical procedures that are carried out by highly trained and qualified health professionals engaged in the practice of medicine.

As we discuss the oversight of laboratory-developed tests, it is crucial that we do not slow innovation or create unnecessary regulatory hurdles. We have got to ask ourselves first, what is the problem that we are trying to solve, and is our response appropriate, and are there unintended consequences that could result?

Requiring premarket review by the FDA will impose new and arguably unnecessary requirements and costs on clinical laboratories, hospitals, and doctors. Although an additional review of certain tests may be warranted, I actually have a greater confidence in a CLIA-centric approach, but there are others—and certainly people on this committee—who suggested a different track. But it remains unclear to me how we can separate the practice of medicine from these laboratory processes, and if we cannot, are we effectively opening the door to the Federal regulation of the practice of medicine? I reject that notion and believe by segmenting this process out has to be the fundamental first step of any proposal.

Let me just reiterate I do want to be involved in this discussion. There is no question in my mind that CLIA can be improved. I was not a fan when CLIA came to my medical practice in 1988. I was not a fan of having to become a CLIA-certified location. I was not a fan of having to apply for a CLIA waiver. But since that time, I think arguably you can make the case that CLIA has been a useful enterprise.

Look, we want doctors and patients to benefit from clinically valid tests, and the current FDA proposal, as such, creates regulatory uncertainty that will not be a catalyst for innovation.

We talk a lot about the Administrative Procedures Act, we talk a lot about notice of proposed rulemaking. This is not coming through the normal regulatory process. It is coming as a guidance. My understanding is to be issued at the end of this year, and like it or not, there you have it.

But, you know, it is hard. On this committee I still retain that romantic notion that our Government exists with the consent of the governed. In my mind that would not include issuing guidances, fiats that are expected to be followed, but rather, you go through the normal administrative procedures, hear people out, and make the best decision based on the information.

Thank you, Mr. Chairman. I yield back the balance of my time.

Mr. PITTS. The Chair thanks the gentleman.

I now recognize the ranking member of the full committee, Mr. Pallone, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Mr. Chairman. I want to also thank Dr. Shuren and Dr. Conway for being here today to discuss the regulation of lab-developed tests.

There has been a lot of discussion over how to appropriately oversee lab-developed tests, and it is important that, as the committee considers this issue, we have a better understanding of the strengths and limitations of both FDA and CMS's authority in this area.

Congress gave FDA authority over lab-developed tests under the Medical Device Amendments in 1976, and at that time, most LDTs were relatively simple tests used more often for rare conditions. Since then, advances in technology and medicine have resulted in LDTs that are increasingly more complex, more readily available to physicians and patients, and used to diagnose and treat a wider range of diseases, including breast cancer and heart disease. LDTs are also increasingly used to provide personalized treatment such as through genetic tests that help physicians to detect the risk of certain diseases earlier or to choose more targeted therapies.

Unfortunately, many of these tests have not been reviewed or cleared by FDA prior to coming to the market to confirm that these tests are accurate, reliable, or provide clinically accurate results. This can result in patients going undiagnosed with certain medical conditions or undergoing treatment that is not medically necessary.

For example, tests have been developed to identify certain gene sequences that can help determine appropriate treatment for ovarian cancer. I am sure many Members here are familiar with the example of OvaSure, which claimed to detect early-stage ovarian cancer in high-risk women. This test, though, was not properly validated and was found to provide high numbers of false positive and false negative results, and this means many women who received a false positive result may have undergone unnecessary surgery to remove healthy ovaries, or some women may have gone undiagnosed after receiving a false-negative result.

Patients deserve to know that the test results they are relying on to diagnose or treat a condition is accurate, a comfort that they do not always have today. And as we have heard from many organizations, patients and their physicians should be able to trust the results of their tests, regardless of how or where a test is developed or performed. It does not make sense to regulate tests differently based on who develops them.

I also believe that we can provide patients and providers with this certainty without endangering or inhibiting the medical innovation that is occurring today. Scientific progress has been made to help facilitate the development and use of personalized medicine, which you all agree is the future of medicine, but this development can only be successful if we know that these complex, sophisticated tests are clinically valid.

So I am glad that today we will have the opportunity to better understand FDA and CMS's authority in this area and hear their perspective on what regulatory changes, if any, are needed to address the future development of lab-developed tests. And I hope moving forward that both agencies will work with the committee on the discussion draft circulated today to ensure that any legislation that moves forward will ensure that LDTs are accurate, reliable, and safe for patients.

I yield back.

[The prepared statement of Mr. Pallone follows:]

PREPARED STATEMENT OF HON. FRANK PALLONE, JR.

Mr. Chairman, thank you for holding today's hearing. I also want to thank both Dr. Shuren and Dr. Conway for being here today to discuss the regulation of lab developed tests.

There has been much discussion over how to appropriately oversee lab developed tests and it is important that as the Committee considers this issue, we have a better understanding of the strengths and limitations of both FDA and CMS's authority in this area.

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I also believe that we can provide patients and providers with this certainty without endangering or inhibiting the medical innovation that is occurring today. Scientific progress has been made to help facilitate the development and use of personalized medicine, which we all agree is the future of medicine. But this development can only be successful if we know that these complex, sophisticated tests are clinically valid.

I am glad that today we will have the opportunity to better understand FDA and CMS's authority in this area and hear their perspective on what regulatory changes, if any, are needed to address the future development of lab-developed tests. I hope

moving forward that both agencies will work with the Committee on the discussion draft circulated today to ensure that any legislation that moves forward will ensure that LDTs are accurate, reliable, and safe for patient use.
I yield back.

Mr. PITTS. The Chair thanks the gentleman.

As usual, all the written opening statements of the Members will be made part of the record.

That concludes the opening statements.

I would like to submit under U.C. request the following documents for the record: a November 16 letter from a number of organizations and laboratory directors, and a November 11 letter from organizations representing patients, advocates, caregivers, and healthcare professionals.

Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. PITTS. On our panel today we have two witnesses, and I welcome them, thank them for coming. First, Dr. Jeffrey Shuren, Director, Centers for Devices and Radiological Health, Food and Drug Administration, Department of Health and Human Services; and Dr. Patrick Conway, Deputy Administrator for Innovation and Quality, and Chief Medical Officer, Office of the Administrator, Centers for Medicare and Medicaid Services, Department of Health and Human Services.

Thank you for coming. Your written testimony will be made part of the record. You will each be given 5 minutes to summarize.

Dr. Shuren, you are recognized for 5 minutes for a summary.

STATEMENTS OF JEFFREY SHUREN, M.D., DIRECTOR, CENTER FOR DEVICES AND RADIOLOGICAL HEALTH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES, AND PATRICK CONWAY, M.D, ACTING PRINCIPAL DEPUTY ADMINISTRATOR, DEPUTY ADMINISTRATOR FOR INNOVATION AND QUALITY, AND CHIEF MEDICAL OFFICER, CENTERS FOR MEDICARE AND MEDICAID SERVICES, DEPARTMENT OF HEALTH AND HUMAN SERVICES

STATEMENT OF JEFFREY SHUREN

Dr. SHUREN. Well, thank you, Chairman Pitts, Ranking Member Green, members of the subcommittee. Thank you for the opportunity to testify today.

We are excited about scientific developments in genomics and molecular biology that are leading to advances in health care, particularly in precision medicine. Getting the right treatment to the right patient at the right time, though, depends upon having accurate, reliable, and clinically valid tests. If not, we give the wrong treatment or we give no treatment, and patients get hurt.

FDA has been regulating in vitro diagnostics for almost 4 decades, and when such a test is made by a laboratory, we call it a laboratory-developed test, or LDT. And the law doesn't distinguish on who makes it. We regulate the test regardless of who makes that test. And we ensure that those tests are analytically and clinically valid.

Now, when we first started regulating IVDs, as a matter of policy, we decided not to actively enforce existing requirements on LDTs because at the time they were generally simple, low-risk tests used on uncommon conditions in often a local setting, typically in a hospital for patients in that hospital. But over time they have come increasingly more complex, higher risk, they are used on common conditions like heart disease, and they may be offered on a national basis. In addition, we have been coming across increasing examples of problematic LDTs. We put out examples of 20 of them just yesterday, and there are others.

As a result of this, the problems we have seen and the increasing complexity, there have been calls on the FDA to actively enforce existing requirements that started in the 1990s, NIH and the Department of Energy. In the 2000s two advisory committees to the Secretary of Health and Human Services called on us to regulate. The Institute of Medicine has asked us to regulate.

So in 2007 we put out draft policy to begin to actively regulate a subset of LDTs, and what the lab community said is don't pick off tests one by one. Please put in place an overarching framework. So in 2010 we had a public meeting to get input, and we were told put in place a risk-based phased-in approach.

And then in response in October of last year we did just that. We put out draft policy to now put in place that framework. And what we heard from the lab community then, oh, no, there are no problems with LDTs. We don't need FDA oversight of anything, maybe a little beefing up on CLIA, but that is it.

And now, just a few months ago, we started to see several proposals come out from the lab community that now, for the first time, acknowledge that LDTs must demonstrate that they are analytically valid and clinically valid, that they should be subject to premarket review, at least moderate- and high-risk tests, the some modifications need to be subject to premarket review, that certain problems need to be reported to the Government, and they need to be under a risk-based approach with a three-tier risk classification system. None of those are currently enforced on them today. They all exist under an FDA framework.

But what most of these proposals except one would do is it would create a duplicative program under CMS and a bifurcated system, leading to more inefficiencies, higher costs, and still putting patients unnecessarily at risk. For example, you can have a conventional manufacturer who makes an IVD we regulated. Now, a laboratory makes a big enough change to it, which laboratories do, and it is regulated by CLIA. Then the original manufacturer makes a change to that test and it bounces back to the FDA. So we will be stuck in a game of regulatory ping-pong, and the real loser here is patients.

Doctors and patients don't care about who makes a test. They do care that their tests are accurate, reliable, and clinically valid.

Now, some labs have already been working with us, and we congratulate them for crossing that picket line. But our message in our invitation to the rest of the lab community is to put down the swords, that for the sake of our patients it is time to end the saber-rattling and instead partner with us moving forward.

Thank you.

[The prepared statement of Dr. Shuren follows:]



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Silver Spring, MD 20993

STATEMENT
OF
JEFFREY SHUREN, M.D., J.D.
DIRECTOR
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE
SUBCOMMITTEE ON HEALTH
COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES
Examining the Regulation of Diagnostic Tests and Laboratory Operations
November 17, 2015

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Jeff Shuren, Director, Center for Devices and Radiological Health, or CDRH, at the Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss the importance of diagnostic tests in medicine and FDA's role in assuring the reasonable safety and effectiveness of these tests; that they are accurate, reliable, and clinically meaningful—regardless of where they are produced—so that patients and their health care providers can rely upon their results to make major medical decisions.

FDA's Statutory Framework for Diagnostic Tests*How the Device Framework Applies to in vitro Diagnostic Devices (IVDs)*

IVDs are tests used in hospitals, doctors' offices, laboratories, and in the home to help health care providers and patients to make the best care management decisions possible, based on accurate, reliable information about a patient. IVDs can be used in the context of acute outbreaks, such as the recent Ebola outbreak, and in the management of chronic diseases like cancer and diabetes. IVDs are a cornerstone of precision medicine, allowing doctors to target therapy to those most likely to respond and avoid unnecessary treatment for those who won't. Because our health care system depends on good information to deploy advanced therapies and new scientific insights into disease and wellness, the success of modern medicine depends on the availability of accurate, reliable diagnostic tests.

FDA regulates IVDs under the flexible, risk-based framework that was put in place by the Medical Device Amendments of 1976 (MDA), which applies to all medical devices intended for human use. Under this framework, FDA assigns IVDs to one of three classes that correspond to the level of risk the IVD presents to patients and the public:

- Class I IVDs encompass about half of all IVDs; these present the lowest level of risk and generally do not require any premarket review by FDA. An example of a Class I IVD is a test system to measure urinary pH.
- Class II IVDs present a moderate level of risk and are generally subject to premarket review; however, they may be exempted when premarket review is not necessary to provide reasonable assurance of safety and effectiveness. Examples of Class II IVDs include blood glucose test strips used by people with diabetes and tests to help doctors diagnose heart failure.
- Class III IVDs present the highest level of risk and are subject to premarket approval and other regulatory controls to ensure these tests can be used safely and effectively. Examples of Class III IVDs include diagnostic tests used to match ovarian cancer patients with a drug regimen.

The primary risk IVDs pose is the risk of an undetected inaccurate test result: a false-positive test result that is not detected could lead to harm from unnecessary medical procedures, delay of necessary medical procedures, and emotional distress. A false-negative result that is not detected could lead to injury, and even death, from unchecked progression of disease, and could have

serious public health ramifications from the preventable transmission of infectious disease. Each of these false outcomes also could result in increased health care costs.

Examples of tests that FDA considers high risk are companion diagnostics that help with the selection of specific treatments for specific patients; with these diagnostics, a faulty test could deprive a patient of a potentially lifesaving therapeutic or could cause a patient to be given an ineffective drug, delaying treatment with the appropriate therapy. An example of a moderate-risk test would be a blood test to aid in the diagnosis of heart failure in the emergency department. Erroneous results from this type of test could also delay appropriate treatment. In both cases, the Agency's premarket review and post-market controls are essential to ensuring patients don't experience grave consequences from inaccurate results. Examples of tests that FDA considers the lowest level of risk include tests for ovulation or certain vitamin deficiencies; we believe about half of all IVDs fall into this category and, as such, we do not require pre-market review.

Under its medical device framework, FDA seeks to apply the level of regulation necessary to establish a reasonable assurance of safety and effectiveness for IVDs, as it does for medical devices generally. For IVDs subject to premarket review, a reasonable assurance of safety and effectiveness generally means that, taking into account the analytical and clinical performance information provided by the sponsor, there is a reasonable assurance that the benefits from the test outweigh the risks it poses and that the test will provide clinically significant results. For moderate-risk tests, the review standard is comparative, and FDA determines whether the test's performance is substantially equivalent to that of a predicate device. And, in cases where there is no existing predicate, novel, moderate-risk tests, if safe and effective, can come to market through our *de novo* down-classification pathway. For high-risk tests, premarket approval is

based on an independent demonstration of safety and effectiveness. *Analytical performance*, also referred to as *analytical validity*, refers to how well the test can detect or measure certain markers in human specimens. *Clinical performance*, also referred to as *clinical validity*, refers to whether the marker has clinical significance, meaning the marker correlates with a disease or condition or with the ability to predict a therapeutic response to a drug.

This assurance of safety and effectiveness is just as important when tests are modified.

Modifications are changes that are made by laboratories and other manufacturers to IVDs, and range from simple changes that may not affect the analytical or clinical performance of the test, such as modifying the salt used in a buffer solution, or making an increase in the number of samples that a laboratory analyzer can process at one time, to highly complex modifications that affect a test's performance—such as changing the measuring range of a marker to detect lower levels or adding a new marker to a panel of markers—or a test's intended use, such as changing the intended use of a Hemoglobin A1c test from monitoring glucose control in someone who already has diabetes to using that test to diagnose diabetes. FDA does not review the vast majority of modifications made to IVDs, or medical devices generally, by manufacturers. However, when a change is critical and affects or could significantly affect the safety or effectiveness of the device—for example, the change elevates the risk of a test or changes the test performance or intended use—it is critical for patients that FDA review the changes to make sure that the test still works. Without oversight, such critical modifications could result in a significant increase in incorrect results. And they could pose the same risk that patients will be exposed to unnecessary treatments or may delay or forgo treatment altogether.

FDA's evidentiary standard for premarket review of devices, including IVDs, is valid scientific evidence—a standard established by Congress in 1976 that still sets the benchmark for

evidence to support premarket submissions. This benchmark ensures that the evidence is of sufficient quality that it can be relied on to determine whether a device should be approved or cleared. Although valid scientific evidence includes prospective clinical trials, the majority of IVDs come to market based on studies using existing human specimens and do not require prospective clinical trials.

How FDA Has Adapted its Oversight to Emerging Diagnostic Technologies

FDA has been highly adaptive with its authority over IVDs, particularly in responding to new diagnostic technologies. FDA has provided clear guidance for companion diagnostics and has suggested a flexible and adaptive regulatory approach for Next-Generation DNA Sequencing devices. These approaches demonstrate the adaptability of the existing regulatory framework and the responsiveness of FDA's device program to regulatory issues presented by these new technologies.

Companion Diagnostics: Companion diagnostic tests play an important role in promptly determining which therapies may be safe and effective for a particular patient, and they are a key component of precision medicine. FDA has approved more than 20 companion diagnostic tests, all of them within the user fee performance goals, ensuring the timely marketing authorization of both the device and drug components. In 2014, FDA issued final guidance describing a clear regulatory pathway for developers of companion diagnostic tests and pharmaceutical manufacturers, receiving strong support from both pharmaceutical and conventional test manufacturers for providing regulatory clarity in this rapidly advancing area of medicine.

Companion diagnostics approved by FDA in recent years include the BRACAnalysis CDx™ test, a laboratory developed test that aids in identifying ovarian cancer patients who may respond

to the drug Lynparza™ (olaparib), based on certain BRCA variants; the THxID™ BRAF Kit, which detects certain mutations in melanoma tissue samples to aid in selecting patients for drug therapy with Tafinlar® (dabrafenib) or Mekinist™ (trametinib); and the theascreen® KRAS RGQ PCR Kit, a test that screens out colorectal cancer patients with genetic mutations known to predict a non-therapeutic response to the biological products Erbitux® (cetuximab) and Vectibix® (panitumumab).

Next-Generation Sequencing: Many newly developed genomic diagnostic tests rely on next-generation sequencing (NGS), an advanced technology, which is poised to become a keystone of precision medicine. NGS tests can rapidly generate an unprecedented amount of genetic data for each patient. Most IVDs are used to detect a single or a defined number of markers to diagnose a limited set of conditions; in contrast, NGS tests can identify thousands or millions of genetic variants in a single run that can be used to diagnose or predict the likelihood of an individual developing one or more of a variety of diseases. An example that demonstrates the potential of NGS for diagnosing disease is the approach FDA has taken for tests to detect mutations that cause cystic fibrosis. FDA provided marketing authorization for an NGS test for cystic fibrosis using innovative approaches to establishing the test's effectiveness in an effort to reduce regulatory burden while continuing to ensure safety and effectiveness. This approach can allow FDA to leverage existing data in high-quality, curated genetic databases as an alternative to conducting new clinical trials, and require targeted analytical performance data for only a subset of variants that would be representative of the device performance.

In summary, the central features of FDA's framework for devices, including IVDs, are a system of device classification that tailors regulation to device risk; a transparent review standard that accounts for the benefits and risks to patients, and range of regulatory controls that together

provide a reasonable assurance of safety and effectiveness; and an adaptive but scientifically grounded evidentiary standard of valid scientific evidence. Patients have benefited from this regulatory model, which has enabled FDA to respond to innovation in rapidly emerging technologies, such as NGS, while ensuring tests used to make treatment decisions for patients are accurate and reliable. To ensure that our health care system continues to benefit from reliable and accurate diagnostic tests, FDA's regulation of IVDs should retain these basic features, including with respect to instances when tests are modified.

FDA's Proposal for Oversight of Laboratory Developed Tests (LDTs)

LDTs are IVDs intended for clinical use and designed, manufactured, and used within a single clinical laboratory. LDTs have all of the same potential uses in health care that IVDs manufactured by traditional manufacturers and approved or cleared by FDA have; like other IVDs, LDTs are used to diagnose conditions, to manage disease, and to gather genetic information to determine the best course of treatment for a patient. Today, many companion diagnostics and other high-risk tests are developed by laboratories. Modern LDTs are often complex, have a nationwide reach, and have high-risk uses, and without oversight could present risks for patients and health care providers who rely on the results of LDTs to make medical decisions. In these respects, LDTs today differ from the relatively simple LDTs in use at the time of the Medical Device Amendments (MDA) of 1976. In many cases, the only difference between many modern LDTs and other IVDs is where they are manufactured, and the accuracy and reliability are every bit as important for modern LDTs as for any other IVD.

Currently, FDA exercises enforcement discretion concerning premarket evaluation and other requirements for LDTs. As such, the Agency generally does not review such tests for clinical

validity prior to such tests being marketed, nor does the Centers for Medicare & Medicaid Services (CMS). While under the Clinical Laboratory Improvement Amendments (CLIA), CMS provides oversight over the pre-analytic, analytic, and post-analytic policies and procedures for laboratory testing on human specimens for medical purposes, and provides minimum standards for the personnel involved in such testing. CMS generally does not delve into ensuring the clinical validity of testing (as CLIA regulates how and by whom the test is conducted and reported out, rather than the scientific principles behind or the clinical validity of the test system itself).

Given the increased complexity of LDTs and the importance of their role in contemporary medical decision-making, FDA issued draft guidance documents describing how it intends to enforce its authorities with respect to LDTs. Examples of concerns that arise from LDTs that are not reviewed for reasonable assurance of safety and effectiveness include the implications for patients who may get incorrect results from faulty tests. For example:

- Ovarian cancer tests have been developed by labs without proper validation to show that the variant they detect is clinically meaningful, and some have been used in clinical practice in the United States. Some of these tests provide very high numbers of false-positive results; some continue to make inflated claims concerning clinical benefit, even after comprehensive evaluations of women with ovarian cancer have failed to find any link between the disease and the genetic variant identified by the LDT. Women who received false-positive results from these tests may have had unnecessary, major surgery to remove their ovaries.

- There are currently on the market several LDTs that test for KIF6, a genetic variant postulated but not proven to predict coronary heart disease (CHD) and the likelihood that a patient will benefit from statins—drugs that reduce the risk of heart attack and death from CHD. Statins also carry side effects that can include muscle pain, cramping, nerve damage, mood, sleep, and cognitive impairment, and, rarely, muscle breakdown leading to kidney failure. One lab sought FDA approval for its KIF6 test; however, FDA determined that a meta-analysis of 19 studies did not support the clinical validity of KIF6, meaning that the data did not adequately support a link between the genetic variant or response to statin therapy. FDA estimates that over 150,000 patients have been given this test; as a consequence, many were likely over- or undertreated with statins. FDA estimates that this resulted in a cost of over \$2.4 billion.

Public health concerns raised by these and other examples of defective LDTs require that FDA implement a more proactive oversight policy. The public must be assured that the tests used in the provision of health care, whether developed by a laboratory or other manufacturer, are accurate and reliable. IVD tests come to FDA for review, in part to try to detect such problems before patients are exposed to them. In light of these concerns, in 2014, after providing a notification to Congress as required by section 1143 of the Food and Drug Administration Safety and Innovation Act of 2012, FDA issued draft guidance documents describing how it intends to enforce its authorities with respect to LDTs.

The draft oversight guidance proposes to phase in enforcement of premarket review requirements for higher-risk LDTs, such as those used to guide treatment decisions, including the many LDTs with the same intended use as cleared or approved companion diagnostics, and proposes to delay

enforcement of the Quality System regulation, at least until the time of enforcement of premarket requirements. In addition, under the draft oversight guidance, FDA would continue to exercise enforcement discretion, with respect to premarket review requirements for low-risk LDTs and LDTs for rare diseases, among others; sponsors of these tests would still need to notify FDA that these LDTs are being offered, as well as providing reports of any adverse events, but would not generally come for premarket review. FDA believes that roughly half of all LDTs would be considered low risk. FDA oversight would be phased in to accommodate lab preparation and transition time. The draft guidance regarding notification and medical device reporting describes an option for clinical laboratories to notify FDA of the LDTs that they manufacture, in lieu of registration and listing, and describes the Medical Device Reporting requirements for clinical laboratories manufacturing LDTs. FDA believes the flexibility built into its proposed approach to LDT oversight is a critical feature of any LDT oversight model.

FDA has completed its review of the public comments on the draft guidance documents that it received through an open public docket and a two-day public meeting, as well as feedback received from several webinars FDA held with stakeholders to discuss concerns and address questions. In response to feedback from stakeholders, FDA is taking several other actions, including:

- High-level engagement with CMS to strengthen coordination of laboratory oversight. FDA also intends to produce a draft guidance document on its quality system requirements for LDTs, to provide clarity for laboratories on how they can leverage compliance with CLIA requirements to satisfy those applicable FDA guidelines;

- Together with CMS, meeting with each of the accrediting organizations and CLIA-exempt state laboratory programs, to identify any potential overlaps between CMS and FDA activities in this area and evaluate if there are areas for streamlining; and
- Ongoing meetings with stakeholders, including laboratories, patients, traditional IVD manufacturers, and medical practitioners.

FDA is committed to developing a final policy for oversight of LDTs that encourages innovation, improves patient outcomes, and strengthens patient confidence in the reliability of these products.

CONCLUSION

I thank the Subcommittee for its leadership in calling this hearing to address the critical role of diagnostic tests in American health care. Mr. Chairman, this concludes my formal remarks. I am pleased to answer any questions the Subcommittee may have.

Mr. PITTS. The Chair thanks the gentleman, now recognizes Dr. Conway, 5 minutes for his summary.

STATEMENT OF PATRICK CONWAY

Dr. CONWAY. Thank you, Chairman Pitts, Ranking Member Green, and members of the committee. Thank you for the opportunity to talk about our work at the Centers for Medicare and Medicaid Services related to ensuring accurate and reliable laboratory testing.

The Clinical Laboratory Improvement Amendments of 1988, commonly referred to as CLIA, of which CMS has primary jurisdiction, created minimum standards of quality for all clinical laboratories in the United States. CLIA successfully worked for approximately 25 years and has contributed to major improvements in the quality of clinical laboratories, promoted accurate testing, and improved patient safety.

As of July of 2015 there were roughly 250,000 laboratories that have registered with CMS and held CLIA certificates. CLIA responsibilities are divided between three agencies: CMS; the Centers for Disease Control, or CDC; and the Food and Drug Administration. CMS conducts laboratory inspections to make sure that laboratories have appropriate controls, expertise, training, and procedures to ensure that tests are accurate and reliable. CMS also approves accreditation organizations and manages the laboratory certification process. CDC conducts laboratory quality improvement studies that guide policy determination and development of laboratory practice guidelines.

FDA's primary responsibility under CLIA is to classify clinical tests into one of three categories—waived, moderate complexity, and high complexity—based on their level of complexity and risk to patients. FDA also has a critical role in determining clinical validity of tests and premarket evaluation. Standards that laboratories must meet under CLIA are based on the complexity of the tests they perform. Laboratories that perform more complex must meet higher standards.

Laboratories that perform moderate- and high-complexity tests must meet requirements on quality assessment, quality control, personnel qualifications and education, general laboratory systems, and proficiency testing, among others. Laboratories that only perform waived tests, simpler tests that pose a low risk to patients, are exempt from most CLIA requirements. In addition, laboratories performing the same tests must meet the same standards, whether located in a hospital, doctor's office, or other site.

This framework is designed to reduce the risk of potential harm and ensure patients receive the same high-quality clinical laboratory testing no matter where the test is performed.

CLIA's provisions apply to all laboratories in the U.S., not just those that receive Medicare payment in order to ensure uniform quality across all laboratories.

CMS enforces CLIA standards by requiring laboratories to obtain certificates in order to operate. CMS conducts onsite surveys prior to issuing a certificate to a lab that performs high- or moderately complex tests. Labs are resurveyed every 2 years, and the surveys

also assist laboratories in improving patient care through education.

Laboratories may also receive CLIA certification by obtaining accreditation from one of the seven private nonprofit accreditation organizations approved by CMS. To receive CMS approval, the accreditation organization requirements must meet or exceed CLIA's requirements.

Moving forward, we believe CLIA and our implementing regulations create the necessary framework to effectively oversee laboratories day-to-day operations and into the future, including those operations that pertain to the use of laboratory-developed tests and other high-complexity tests. We have several principles that have helped guide our work in CLIA, which may also be useful when informing future efforts of this committee.

First, we aim to prevent duplicative oversight efforts across agencies. CLIA requires coordination across CMS, FDA, and CDC. We have worked to ensure our oversight efforts are consistent and complementary and not duplicative. In doing so, we have ensured that we take advantage of the unique expertise of each agency and its staff.

Second, we focus on our agency's oversight strengths. When CLIA was implemented in the early 1990s, the responsibility to conduct certifications of laboratories was a natural fit for CMS because of our survey and certification experience. On the other hand, CMS does not have scientific staff capable of reviewing complex medical and scientific literature in determining clinical validity. This expertise resides within the FDA, which assesses clinical validity in the context of premarket reviews and other activities aligned with their regulatory efforts under the Food, Drug, and Cosmetic Act.

Third, we value our relationship with our private accreditor organizations and State-based partners. These organizations play an important role in evaluating and certifying laboratories.

Fourth, we take targeted, risk-based approaches to oversight to improve patient safety without creating burdensome administrative requirements. We believe the current approach in which laboratories must meet higher standards if they are to perform more complex tests has paid dividends in improving the quality of the testing process.

Finally, as a practicing physician who works clinically on weekends, I know the importance of tests being assessed for clinical validity, as well as the need for assessment for laboratory standards. FDA and CMS can work together utilizing their respective authorities and strengths to assess premarket clinical validity and laboratory standards respectively.

Thank you again for the opportunity to discuss CMS's work related to ensuring accurate and reliable laboratory testing. I look forward to your questions. Thank you.

[The prepared statement of Dr. Conway follows:]

STATEMENT OF

PATRICK CONWAY, MD, MSc

ACTING PRINCIPAL DEPUTY ADMINISTRATOR,
DEPUTY ADMINISTRATOR FOR INNOVATION AND QUALITY, AND
CHIEF MEDICAL OFFICER,
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ON

“EXAMINING THE REGULATION OF DIAGNOSTIC TESTS
AND LABORATORY OPERATIONS”

BEFORE THE

UNITED STATES HOUSE COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON HEALTH

NOVEMBER 17, 2015

Statement of Patrick Conway, MD, MSc
House Committee on Energy and Commerce, Subcommittee on Health
Hearing on “Examining the Regulation of Diagnostic Tests and Laboratory Operations”
November 17, 2015

Chairman Pitts, Ranking Member Green and Members of the Committee, thank you for the opportunity to talk about our work at the Centers for Medicare & Medicaid Services (CMS) related to ensuring accurate and reliable laboratory testing. The Clinical Laboratory Improvement Amendments of 1988 (CLIA)¹, over which CMS has primary jurisdiction,² created minimum standards of quality for all clinical laboratories in the United States, leading to improved patient safety and better, more effective care for all Americans.

CLIA established quality standards for all laboratory testing performed on human specimens for the purpose of providing information for the diagnosis, prevention, or treatment of disease, or assessment of health. In the late 1980s, laboratories’ inaccurate reading of Pap tests contributed to potentially preventable harm from cervical cancer.³ In response, Congress enacted CLIA to address concerns about the rapid growth in unregulated laboratories and, in particular, the lack of workload limits for individuals reading Pap tests – an important patient safety issue associated with laboratory testing.⁴

CLIA has successfully worked for nearly 25 years, contributing to major improvements in the quality of clinical laboratories, promoting more accurate testing, and improving patient safety. Due to the long and consistent operation of the program, the vast majority of laboratories understand, appropriately implement and use CLIA requirements to enhance the quality of their laboratory testing. As of July 2015, there were roughly 250,000 laboratories that had registered with CMS and held CLIA certificates. Because of CMS’ extensive education efforts with

¹ Public Law 100-578 <http://www.gpo.gov/fdsys/pkg/STATUTE-102/pdf/STATUTE-102-Pg2903.pdf>

² The Centers for Medicare and Medicaid Services, the Food and Drug Administration, and the Centers for Disease Control and Prevention all have specific roles in assuring quality laboratory services under CLIA.

³ Bogdanich W. Lax Laboratories: The Pap Test Misses Much Cervical Cancer through Labs’ Errors. Wall Street Journal, Nov. 2, 1987: 1,20.

⁴ Congressional Research Service Report ‘Regulation of Clinical Tests: In Vitro Diagnostic (IVD) Devices, Laboratory Developed Tests (LDTs), and Genetic Tests’ December 17, 2014

laboratories, only 90 were subjected to sanctions for non-compliance in the previous year.⁵ In addition, laboratories continue to improve their performance on proficiency tests (PT), which are important quality improvement tools that help laboratories verify that their test results are accurate and reliable. Over the past 10 years, PT “failure rates”⁶ have steadily decreased from nine percent in 2005 to three percent in 2014.

CLIA Standards and Laboratory Oversight

CLIA, and the regulations that implement it, created a system of laboratory oversight that is primarily based on test complexity. CLIA responsibilities are currently divided between three agencies: CMS, the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA). CMS conducts laboratory inspections to make sure that laboratories have appropriate controls, expertise, training, and procedures to ensure that test results are accurate and reliable. CMS also manages the approval of accreditation organizations and the certification of laboratories. CDC has shared responsibility with CMS for CLIA technical standards development and revision and for performing regulatory impact analyses. CDC’s role also includes conducting laboratory quality improvement studies that guide policy determination and development of laboratory practice guidelines (*e.g.*, best practices). In addition, CDC monitors PT practices, develops and distributes educational resources to laboratory professionals, and manages the Clinical Laboratory Improvement Advisory Committee (CLIAC), which advises the Federal Government on CLIA issues.

FDA’s primary responsibility under CLIA is to classify clinical tests into one of three categories (waived, moderate-complexity and high-complexity) based on their level of complexity and risk to patients. All tests introduced in the United States are high-complexity by default unless FDA categorizes a test as moderate or waived complexity. FDA does not categorize tests developed by and used within a single laboratory, known as laboratory-developed tests (LDTs). Thus, by default, they are considered to be high-complexity tests.

⁵ 194 laboratories were *proposed* for sanctions in 2014 but only 90 were actually subjected to sanctions. The others were able to improve their processes to demonstrate compliance.

⁶ Failures occur when a laboratory’s submitted proficiency testing results are inaccurate or not reliable. Low failure rates indicate a high level of consistency, accuracy and reliability in testing.

Standards that laboratories must meet under CLIA are based on the complexity of tests they perform – laboratories that perform more complex tests must meet higher standards. Laboratories that perform moderate- and high-complexity tests must meet requirements on quality assessment, quality control, personnel qualifications and education, general laboratory systems, and proficiency testing, among others. Laboratories that perform only waived tests – which are cleared by FDA for home use, and either are simple and accurate with a negligible risk of erroneous result or pose a low risk to patients should they be performed incorrectly⁷ – are exempt from most CLIA requirements. Examples of waived tests include blood glucose testing using monitors that have been cleared for home use, urine pregnancy tests, and other urine dipstick tests.

Further, laboratories performing the same test must meet the same standards, whether located in a hospital, doctor's office, or other site. This framework is designed to reduce the risk of potential patient harm and ensure patients receive the same high quality clinical laboratory testing no matter where their test is performed. CLIA's provisions apply to all laboratories in the United States, not just those that receive Medicare payment, in order to ensure uniform quality across all laboratories.

It is important to note that FDA has regulatory authorities, apart from CLIA, governing the quality of laboratory tests. These multi-agency efforts are different in focus, scope, and purpose, but they are intended to be complementary in assuring safe and high quality laboratory services. The joint efforts of CDC, FDA, and CMS have resulted in improved clinical laboratory operations.

Laboratory Certification

CMS enforces CLIA standards by requiring laboratories to obtain a certificate in order to operate.⁸ Laboratories that perform moderate and high complexity tests need to obtain a Certificate of Compliance (COC) or a Certificate of Accreditation (COA), demonstrating that they adhere to all CLIA requirements. CMS conducts on-site surveys prior to issuing a COC to

⁷ 42 CFR 493.15

⁸ There are five types of certificates: Certificate of Waiver; Certificate for Provider-Performed Microscopy Procedures (a type of moderate-complexity test); Certificate of Registration (COR); Certificate of Compliance; and Certificate of Accreditation.

confirm a laboratory's compliance with the requirements.⁹ The surveys also assist laboratories in improving patient care through education and by emphasizing requirements that directly impact the accuracy and reliability of the laboratory's test performance.

Laboratories holding COCs are surveyed against CLIA regulations every two years. Although CMS has Federal surveyors, which perform on-site CLIA surveys of laboratories across the country, most laboratories are surveyed by state-health-department representatives who coordinate their reviews with CMS.

Laboratories may also receive CLIA certification by virtue of obtaining accreditation (under a COA) from one of seven private, non-profit accreditation organizations approved by CMS. The accreditation organization also inspects laboratories once every two years. To receive CMS approval, the non-profit accreditation organization's requirements must meet or exceed CLIA program condition-level requirements. Periodically, each organization must receive re-approval to ensure it maintains standards that are equal to or more stringent than CLIA regulations.¹⁰ The re-approval review also includes an on-site visit to evaluate the accreditation organization's laboratory oversight practices. In addition to the re-approval process, CMS evaluates each accreditation organization's performance through a validation survey where we compare the results of the most recent survey performed by the accreditation organization to a survey performed by CLIA surveyors.

Laboratories that only perform waived tests receive a Certificate of Waiver (COW). On-site surveys are not required for a COW laboratory unless there is a complaint. In addition, laboratories that perform only waived tests and certain moderate complexity microscopy procedures can receive a Certificate of Provider-Performed Microscopy Procedures (PPM).¹¹ As with waived tests, routine on-site surveys are not required for laboratories with a Certificate of PPM. However, a PPM laboratory may be subject to surveys if a complaint is received.

⁹ A COR provides temporary certification for a laboratory to conduct moderate and high complexity tests while it completes the certification process. The COR expires after the earlier of two years or when the laboratory meets certification requirements.

¹⁰ 42 USC 236a, (e)(2)(A)(ii)

¹¹ As of July 2015, 174,122 laboratories performed only waived tests and had received a COW, 18,505 laboratories have received a COC, 16,431 have been accredited and received a COA, and 35,150 have received a Certificate of PPM. Link: <http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/statupda.pdf>

Proficiency Testing

CMS' laboratory operations oversight activities include monitoring laboratory performance on PT. CMS requires laboratories conducting moderate or high complexity testing to participate in PT for certain tests. A CMS-approved PT program sends the laboratory a set of blind samples roughly three times per year. The laboratory tests the samples in the same manner as it tests patient specimens and reports the results back to the PT program. The PT program grades the results and sends the laboratory scores reflecting how accurately the laboratory performed the testing. PT programs undergo annual and ongoing regulatory review by CMS.

A CLIA Performance Goal study was conducted in 2003 on the number of laboratories properly enrolled and participating in PT and PT performance (*i.e.*, the number of laboratories enrolled in PT with no failures) from 1995 through 2003. The study showed a significant increase in PT enrollment, from 89.6 percent in 1995 to 97.2 percent in 2003, and significant improvement in PT performance, from 69.4 percent in 1995 to 92.8 percent in 2003. A 2010 CDC Report¹² on PT performance also showed improvement in PT performance scores for approximately 30,000 laboratories.

CMS also has worked to clarify aspects of the PT program in response to stakeholder questions, and has implemented several revisions to the requirements. In May 2014, CMS issued a final regulation¹³ to promote program efficiency and reduce burden, including under CLIA. We issued separate regulations in July 2014 to implement the Taking Essential Steps for Testing Act¹⁴. Together, these rules clarified specific types of PT referral (when a laboratory sends a PT sample to another laboratory for analysis) and increased flexibility in enforcement for laboratories that engage in this practice.

Laboratory-Developed Tests

FDA defines an LDT as an in vitro diagnostic test device that is intended for clinical use and designed, manufactured, and used within a single laboratory (*i.e.*, a laboratory with a single CLIA certificate). These tests are also sometimes called “in-house developed tests.” LDTs are

¹² <http://www.ncbi.nlm.nih.gov/pubmed/20441507>

¹³ <http://www.gpo.gov/fdsys/pkg/FR-2014-05-12/pdf/2014-10687.pdf>

¹⁴ Public Law 112-202

“devices,” as defined by the Food, Drug and Cosmetic Act, and are therefore subject to regulatory oversight by FDA. However, as noted above, FDA currently exercises its enforcement discretion with respect to LDTs.

Under CLIA, when a laboratory uses a test system that has not received FDA clearance or approval, such as an LDT, the laboratory treats the test as a high-complexity test. CLIA does not require premarket review of LDTs; the law merely regulates how and by whom the test is conducted and reported out, rather than the scientific principles behind or the clinical validity of the test system itself.

As with all high- and moderate-complexity testing, a laboratory may not release any high-complexity or moderate-complexity test result, including an LDT test result, prior to establishing certain performance characteristics relating to analytical validity for the use of that test system in the laboratory’s own environment.¹⁵ These performance-specification assessments measure the test’s: (1) accuracy (whether the test correctly measures the specific analyte when compared to a standard/reference); (2) precision (whether the test result is reproducible when repeated); (3) reference range (whether the normal range of results is based on the laboratory’s specific patient population); (4) reportable range (the lower and higher limits that the test can accurately report); (5) analytic sensitivity (minimum detection limits or how much of the analyte must be present to be measured); and (6) analytic specificity (the extent to which the method measures the analyte for which it is reporting results) that can be achieved using the given test system in that laboratory’s physical environment. The results can then be compared to the manufacturer’s expected performance specifications, and ultimately be used by the laboratory director as a basis for rejecting or accepting use of that test system in that laboratory.

Again, other than requiring that lab directors ensure that the test systems they select meet performance specifications that will ensure quality results, CLIA does not regulate the scientific principles behind or the clinical validity of any test – that is, the ability of the test to identify, measure, or predict the presence or absence of a clinically relevant condition or predisposition in a patient. FDA is authorized to evaluate the clinical validity of a test under its premarket clearance and approval processes, as part of its responsibility for assuring the reasonable safety

¹⁵ 42 CFR 493.1253(b)(2) Establishment of Performance Specifications.

and effectiveness of medical devices, generally. As a result, FDA has built substantial experience and expertise in this area, and CMS has generally deferred to FDA on how best to ensure the clinical validity of test systems.

Moving Forward

CMS is committed to ensuring high quality, accurate, and reliable laboratory testing by assuring that laboratories have appropriate controls, expertise, training, and procedures. We believe CLIA and our implementing regulations create the necessary framework to effectively oversee laboratory's day-to-day operations today and into the future – including those operations that pertain to the use of high-complexity tests, including LDTs.

In addition, there are several principles, noted below, that help guide our work on CLIA, which may also be useful in informing any future efforts by the Committee in this area.

- First, we aim to prevent duplicative oversight efforts across agencies. CLIA requires effective coordination across CMS, FDA, and CDC. We have worked hard to ensure our oversight efforts are consistent and complementary with other related but distinct regulatory schemes. And, in doing so, we have ensured that we take advantage of the unique expertise of each Agency and its staff.
- Second, we focus on building on our Agency's oversight strengths. When CLIA was implemented in the early 1990s, the responsibility to conduct certifications of laboratories was a natural fit for CMS because of our survey and certification experience.¹⁶ On the other hand, CMS does not have a scientific staff capable of determining whether a test is difficult to successfully carry out or likely to prove detrimental to a patient if carried out improperly. This expertise resides within the FDA, which assesses clinical validity in the context of premarket reviews and other activities aligned with their regulatory efforts under the Food, Drug, and Cosmetic Act.
- Third, we value our relationship with our private sector accreditation organizations and state-based partners. These organizations play an important role in evaluating and certifying laboratories – roughly 16,400 laboratories performing non-waived testing in

¹⁶ CMS requires other providers – such as hospitals, nursing homes, physician practices and others – to meet CLIA standards and, in some cases, undergo a CMS- or accreditor-led survey.

the United States are certified through an accrediting organization.¹⁷ In addition, laboratories in two states¹⁸ receive exempt status because these states have standards that are at least as stringent as CLIA. We believe it is important to preserve these organizations' ability to use private sector and state-driven approaches to build on the minimum standards established by CLIA.

- Fourth, we take targeted, smart approaches to oversight to improve patient safety without creating burdensome administrative requirements in regard to the areas over which we have authority. We believe the current approach – in which laboratories must meet higher standards if they perform more complex tests – has paid dividends in improving the quality of testing processes.

Thank you, again, for the opportunity to discuss CMS's work related to ensuring accurate and reliable laboratory testing. We look forward to continuing our work with the Committee to promote high-quality laboratory testing for all Americans.

¹⁷ <https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/statupda.pdf>

¹⁸ New York and Washington. Laboratories in NY have a partial exemption: all Physician Office Labs (POLs) fall under CLIA and are inspected every two years by CLIA surveyors. Any laboratory in NY that is not a POL falls under NY State licensure requirements and these are inspected by NY State CLEP (Clinical Laboratory Evaluation Program) surveyors. There are approximately 4,150 laboratories under the NY exempt state program and 4,023 laboratories under the WA exempt state program.

Mr. PITTS. The Chair thanks the gentleman, both witnesses for your opening statements. I will begin the questioning. I will recognize myself 5 minutes for that purpose.

The discussion draft, which the committee circulated before the hearing, divides FDA and CMS responsibilities based upon the type of activity being conducted by the regulated entity. FDA would regulate test development activities in a risk-based manner, and CMS would regulate lab operations.

Unlike the discussion draft, some alternative proposals being floated would divide regulatory oversight between CMS and FDA depending on the type of test.

I would like each of you to respond. Dr. Shuren, would you comment on the implications of an approach that would divide oversight between CMS and FDA based on the type of test, as opposed to the type of activity?

Dr. SHUREN. So such a system is going to lead to inefficiencies. It is going to lead to inconsistent standards, treating the same kind of test differently depending upon who makes the test. And as a result, you can go to one institution, get a test, and it is regulated by FDA. You can get the same kind of test across the street and it is regulated by CMS. And the people who are put at risk, it is patients.

If we are going to assure that tests work, we need one unified system that we are applying consistent standards and we are assuring that those tests are accurate, reliable, and clinically valid.

Mr. PITTS. Dr. Conway, would you comment on that, the implications of an approach that divides oversight between CMS and FDA based on the type of test, as opposed to the type of activity?

Dr. CONWAY. Yes, I agree with Dr. Shuren. The concern here is we want to reduce and avoid duplication and ensure coordination across agencies. You know, from a CLIA construct we really are focused on post-market review, laboratory by laboratory, and we are really focused on the things such as the protocols in place in the laboratory, the equipment and equipment maintenance, the training of staff and personnel. So CLIA's focus really is on that laboratory-by-laboratory assessment of quality standards.

Mr. PITTS. And expand a little bit more on whether such an approach would create administrative duplication or any inconsistencies, Dr. Shuren?

Dr. SHUREN. That is correct. It will create inefficiencies and higher costs because essentially we have duplicative systems in FDA and CMS, and the real distinction is just simply who makes the test, which doesn't make sense. And we will have inconsistent standards. We can try to coordinate between ourselves, but quite frankly, that becomes much more challenging as tests also begin to bounce between FDA oversight and CMS oversight.

Mr. PITTS. OK. Dr. Conway, you stated in your testimony that "CMS does not have a scientific staff capable of determining whether a test is difficult to successfully carry out or likely to prove detrimental to a patient if carried out improperly. This expertise resides within the FDA." From your perspective at CMS, what would be the impact on patients if FDA were precluded from reviewing the clinical validity of most LDTs?

Dr. CONWAY. Yes. So as Dr. Shuren mentioned, I think the challenge is if FDA is not reviewing the test in a premarket manner for clinical validity, then our surveyors in CLIA are not assessing clinical validity. They are assessing laboratory practices and the protocols and standards in those laboratories. So as a practicing physician, it is critical, as Dr. Shuren said, that we know that a test is clinically valid, meaning it is truly detecting the presence or absence of disease. Therefore, the premarket review by FDA is important.

Mr. PITTS. Now, some stakeholders have said that CMS should be tasked with reviewing tests for clinical validity. What are your thoughts on that approach?

Dr. CONWAY. So our survey staff are not trained to assess clinical validity, and then let me build on that. Our survey staff are trained in laboratory protocols, equipment, standards around those protocols, whereas—and Dr. Shuren can certainly speak directly to FDA's staff—is, you know, physicians, Ph.D.'s, biostatisticians who are trained in assessing the scientific literature in its entirety and assessing clinical validity.

Mr. PITTS. Now, some stakeholders have suggested that CMS should regulate tests developed by labs. FDA should regulate tests developed by manufacturers. Some have proposed carving out a role for FDA only when a test developer chooses not to publicize their methodologies. Shouldn't the test's impact on the patient, regardless of who developed it, be the primary factor in developing a regulatory framework? Dr. Shuren and then Dr. Conway.

Dr. SHUREN. Well, we agree that this should be a risk-based framework. We also think that you should have one agency that is reviewing those tests to assure that they are accurate, reliable, and clinically valid. That assures consistency.

But also, one of the things we have found is when someone makes a test, another lab or another entity makes a similar test, we learn from that, and we sometimes identify problems or common problems and we are able to feed that back to test developers. If you split it between two agencies, we are going to lose all that learning that ultimately benefits innovation and benefits patients.

Mr. PITTS. Dr. Conway, do you want to comment?

Dr. CONWAY. So I agree with Dr. Shuren. I believe one agency doing the premarket review, as Dr. Shuren said, and that agency being FDA, makes sense given the training and expertise. We also, as you have heard, have a principle of coordination and using each agency's expertise. CMS's focus and expertise is in the area of laboratory assessment, laboratory by laboratory, on protocols, equipment, et cetera.

Mr. PITTS. My time is expired. The Chair recognizes the ranking member, Mr. Green, 5 minutes for questions.

Mr. GREEN. Thank you, Mr. Chairman.

I would like to ask unanimous consent to submit a letter from the American Cancer Society Cancer Action Network for the record.

Mr. PITTS. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. GREEN. Dr. Shuren, with other medical devices, FDA has proposed regulating lab-developed tests based on the risk of the test to the patient and the public. Under proposed FDA would clas-

sify LDTs into three risk classes: low, moderate, and high. Can you explain how FDA proposes to finding the low, moderate, and high risk in the agency's framework describing how premarket or post-market requirements would vary among these risk classes?

Dr. SHUREN. So we look at risk based upon what the risk is to patients if that test provides a false result, an incorrect result. And we estimate that for low-risk tests we do not conduct premarket review because they are so low risk. We think about 50 percent of the tests out there—that has been our experience—are low risk. And then we conduct premarket review for high-risk and moderate-risk tests. High-risk tests are only about 1 to 2 percent of the tests out there, moderate risk about 48 percent.

And the data needed to demonstrate analytical and clinical validity differs depending upon the risk of the disease. There is less burden involved when it is a less-riskier test rather than we are reviewing, and that is the risk-based approach that we apply.

Mr. GREEN. FDA's approval standard for drugs and medical devices safe and effective, can you just please discuss the approval standard FDA has proposed using for the regulation of lab-developed tests?

Dr. SHUREN. So we would apply the same standard we would apply to in vitro diagnostic tests that are not made by a lab, that they are analytically valid, they are clinically valid, and they are safe to use under their conditions to use. That means they are accurate on what they measure, they are reliable, and they will identify they in fact do identify a disease.

Mr. GREEN. Companion diagnostics is an area of great interest and enthusiasm. Can you talk about how the FDA views this category of tests, in particular the level of risk posed to patients and how they would be treated under the proposed guidance?

Dr. SHUREN. So companion diagnostics are increasingly playing a bigger role in health care. Essentially, companion diagnostic is a test where the safety and effectiveness of the therapeutic depends upon the diagnostic because the diagnostic informs whether or not that patient should receive a particular treatment. And that is why it is critically important that those tests truly work, because if not, then patients are not getting the right treatment or they may be getting no treatment at all.

For example, we had a test for providing treatment for women with breast cancer and found that LDTs in the past were producing as much as 20 percent of them incorrect or inaccurate results. That means that women who should have gotten treated with the right treatment were not. And that is preventable.

Mr. GREEN. OK. Thank you. Dr. Conway, I want to thank you also for participating. As you are aware, following the release of the FDA's guidance on enforcing requirements for lab-developed tests, a number of stakeholders called for enhancement of CLIA as a more appropriate way to regulate the tests. And I appreciate your testimony on outlining the difference between FDA and CMS authority over the tests.

One of the key differences is the fact that under CLIA CMS does not review a test for the clinical validity, that is, accuracy on which the test identifies measures or predicts the presence and absence of a clinical condition or predisposition to a patient. Rather, CMS

reviews look at analytical validity. You noted that the experience and expertise in assessed clinical validity resides instead with the FDA.

Despite CMS stating on more than one occasion that the agency does not have the experience or the scientific expertise to assess clinical validity in premarket review, many stakeholders continue to advocate for additional authority in that area for CMS. Can you please discuss further CMS capabilities in implementing regulations for overseeing LDTs, and can you also please comment on whether CMS would have the capability of conducting any type of premarket review or regulatory review of LDTs?

Dr. CONWAY. Yes. So our framework that we believe is working well now is CLIA is focused on assessment of the protocols, the standards, the equipment, the training, and the personnel. Even in analytic validity, we are simply looking at, you know, does the lab test detect the analyte described? That is very different than clinical validity, which is assessing whether, you know, the test reliably and accurately detects the presence or absence of disease, as Dr. Shuren said.

You know, the majority of our staff are—you know, we have got approximately 25 people in the central office running CLIA, a little over 100 surveyors across the States, all of the States. They are generally medical technologists, former laboratory personnel trained to assess laboratory by laboratory. They are not trained to assess premarket scientific literature and determine clinical validity.

Mr. GREEN. OK. Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman and now recognizes the vice chair of the full committee, Mrs. Blackburn, 5 minutes for an opening statement.

Mrs. BLACKBURN. Thank you, Mr. Chairman.

Dr. Shuren, looking at the LDT guidance, do you plan to finalize that guidance that you issued last year? Do you plan to finalize that this year?

Dr. SHUREN. Yes, we do plan to finalize that.

Mrs. BLACKBURN. OK. When?

Dr. SHUREN. In 2016.

Mrs. BLACKBURN. OK. So basically you are going to put it off another year?

Dr. SHUREN. I don't get to determine when, but the plan is to put it out in 2016.

Mrs. BLACKBURN. In 2016. Early or late?

Dr. SHUREN. Hopefully earlier than later.

Mrs. BLACKBURN. OK.

Dr. SHUREN. I wish I could give you an answer. Again, it is so far above my pay grade. I don't even know the people who make the decisions.

Mrs. BLACKBURN. Well, my goodness, we need to have a meet-and-greet over at the FDA and see if we can't get some wheels turning over there. We should help with that.

Let me ask you this. As you finalize that guidance, do you intend to use what I think is the outdated 1970s definition of a medical device in order to regulate the LDTs?

Dr. SHUREN. Well, so that definition also includes a distinct definition for in vitro diagnostics, which then incorporates laboratory-developed tests. It does not distinguish who makes the tests.

Mrs. BLACKBURN. OK. Let me ask you this. Each improvement in an LDT technology or an upgrade or an update, will that need to go back through the medical device approval process?

Dr. SHUREN. No. Most modifications to tests are not reviewed by FDA. We only focus on those that have the really big impact, yes.

Mrs. BLACKBURN. OK. Do you intend to add to the rapid growth of healthcare costs by taxing LDTs as medical devices in addition to charging the innovators the user fee?

Dr. SHUREN. So we are not responsible for administrating the device tax. That is IRS. We have nothing to do with it.

That said, one of the reasons we put in place that laboratories could notify us about their tests as opposed to registering and listing was that it would not trigger the device tax.

Mrs. BLACKBURN. I think your guidance informs the IRS, though, is that not correct?

Dr. SHUREN. No, the IRS would look separately to if that device has listed.

Mrs. BLACKBURN. OK. I want to thank you for the report that you sent to the Congress last night. It was an interesting read. And what I found most interesting about it was what was left out and that you didn't discuss the FDA front-end process, which deserves some attention and some discussion, specifically the PREDICT program. Twenty-eleven this was put in place. It is a compliance program. It is an artificial intelligence program that is supposed to identify high-risk shipments at our ports of entry. And the problem with PREDICT is that it is significantly delaying the shipment of needed medicine and medical supplies. Medical shipments are often sent by express service to get them to patients in time for critical usage. And once a shipment is held up by PREDICT, almost all of them are subsequently released without any physical inspection.

So when you look at it from the outside, Dr. Shuren, what it appears to be and the impression is that the bureaucracy of the FDA is keeping medicines and medical supplies from patients because of concerns that there may have been contamination in some cilantro that was in the very same shipment. And I would really like to see the FDA spend the effort to fix this before they try to regulate another area of commerce.

I noticed in that report also that it is based on 20 case studies. And how often does the FDA use case studies as sufficient evidence to approve or deny a medical therapy?

Dr. SHUREN. So in terms of approval, we don't tend to rely on an example. We have used a series of case studies as part of support for valid scientific evidence as we have approved certain tests or other products.

I will note one thing about the cases, too, we put out yesterday. One of the challenges is that we don't have post-market surveillance in place for laboratory-developed tests as we do for tests made by other manufacturers. And as a result, it is very hard to identify when problems arise. And yet we know on the IVD side, when made by conventional manufacturers, we do detect problems,

the manufacturers detect problems, and they fix them because that is in place.

One of the other features in the FDA system is the post-market surveillance to identify problems and to fix problems, and that is just as important as premarket review to prevent faulty tests from getting on the market in the first place.

Mrs. BLACKBURN. Well, as I yield back my time, I hope that you will fix PREDICT. I yield back.

Mr. PITTS. The Chair thanks the gentlelady and now recognizes the gentlelady from California, Mrs. Capps, 5 minutes for questions.

Mrs. CAPPS. Thank you both, each of you, for your testimony, and thank you, Mr. Chairman, for putting together this hearing. I appreciate the opportunity to further discuss the strengths and challenges, have a real conversation about laboratory-developed tests as they guide medical decision-making by patients and providers. There are a lot of question marks and a lot of concern about where do we go from here, how do we dovetail these two agencies and giving the best outcome the patients.

I recognize there are many perspectives in this space. I appreciate this conversation to try to illuminate some of the issues. Over the years, it goes without saying these tests have come more tailored and more elaborate, and this conversation is important to ensure that these tests do produce meaningful and reliable results for those who trust them.

Dr. Conway, I will turn to you first. In your testimony you note that there are six key performance specification assessments for lab-developed tests: accuracy, precision, reference range, reportable range, analytic sensitivity, analytic specificity. This committee has heard a lot about how different research institutions are driving the future of medicine toward more personalized medicine. This has been particularly true in the field of cancer where the development of multi-gene panels is being used to identify important molecular characteristics of a tumor.

And my question to you is whether the current CLIA regulations ensure these gene panels developed by different institutions or manufacturers will produce the same results? For example, if I am a patient and I am tested with hospital A's gene panel, how do I know I would get the same result if I am tested with hospital B's gene panel? Would each hospital reach the same treatment decision, and where does this lead us?

Dr. CONWAY. Yes, you have highlighted—thank you for the question, and you have highlighted one of the challenges. And Dr. Shuren could certainly speak more.

You know, our assessment of analytic validity is laboratory by laboratory where we are looking at the areas you described and the laboratory director's documentation, that they are following a protocol to detect the appropriate analyte.

And you highlighted a great example, genetic testing. It is not assessing whether different genetic testing kits or combination of tests are detecting the disease with the same clinical validity and rigor. So you could in fact in the current framework, without premarket assessment of clinical validity, have different tests giving different answers to clinicians that could drive treatment that is in-

appropriate, which is why we think the assessment of premarket clinical validity in this area is critical and important.

Mrs. CAPPS. So that leads me to focus now with you, Dr. Shuren. Many have argued that there is no need for greater FDA oversight of lab-developed tests, as we have not had the same types of problems with LDTs as we have had with drugs such as the outbreak of adverse events associated with use of contaminated heparin, for example, or adverse events associated with contaminated compounded drugs. They assert that if there are greater health risks associated with LDTs, we would have heard about them.

I am not sure you agree, but it is clear to me from the report that FDA released yesterday that lab-developed tests do present real risks to patients. Can you please explain whether or not you agree with this criticism that came out? Would healthcare providers and patients necessarily know if tests were not giving good advice for clinical decisions?

Dr. SHUREN. I don't agree with that criticism. And doctors and patients would not know who made the device and whether it is one that was approved by FDA or it was one that was not approved by FDA. Quite frankly, the reason you don't see as many problems, you don't have the systems in place to identify them. So, for example, for IVDs we regulate, in 2014 we had over 300 recalls. It is not unusual.

Things change, problems arise, but you need the systems to identify the problems and to fix them. And we have some labs who have submitted their tests to us, and we have approved or cleared some LDTs. And when they put the systems in place, these started to identify problems. One of them has already had eight recalls, but they only found the problems because they put in the systems that they should have in place.

Mrs. CAPPS. Well, now, how can patients—I am just about out of time, but how can patients, providers, and payers be assured that the tests they are paying for are providing real value and enhancing the care of patients?

Dr. SHUREN. Well, that is why we would like to have a uniform, consistent approach to diagnostic tests, regardless of who makes them. That information will be made available to the public so they know what tests have been approved. There is information about what those tests are for. The makers have to put out information that explains its performance characteristics, its intended use, how to use it properly, and all that will provide necessary information to doctors and patients so they can use those tests appropriately.

Mrs. CAPPS. Thank you.

Dr. SHUREN. Right now, they can't.

Mrs. CAPPS. OK. It sounds like we need a follow-up. I yield back.

Mr. PITTS. The Chair thanks the gentlelady and now recognizes the chair emeritus of the full committee, Mr. Barton, 5 minutes for questions.

Mr. BARTON. Thank you, Mr. Chairman. I want to thank both our witnesses for attending today. I appreciate the subcommittee chairman, the full committee chairman issuing the proposal as a discussion draft, which to me means that their minds are still open and that we can make some changes and things of this sort.

I am one of those skeptics that Mrs. Capps just talked about. I am not sure that we need to get more Federal regulation. I don't necessarily think more Federal regulation is going to give us a safer, more efficacious result.

So I guess my first question to either of you gentlemen would be what is the real problem? I mean why in the world would a laboratory develop a test that wasn't safe and accurate? My office is not being overrun with phone calls or emails from doctors, patients, hospitals, advocacy groups that there is some terrible laboratory diagnostic test out in the marketplace.

Dr. SHUREN. But those tests are out on the marketplace. So, for example, a test was developed for something called KIV 6. It was supposed to predict the risk of heart disease and response to statin treatment. And the lab came out with it, promoted it, said they had studies, but then subsequently good studies were performed and in fact found that there was no association between KIV 6 and those conditions. And by the time it came out, though, over 150,000 people had the tests performed. We estimated the cost to our healthcare system was over \$2 billion. That is not money we can afford to waste on bad testing.

Mr. BARTON. And what happened—

Dr. SHUREN. So what happened—

Mr. BARTON. I assume that test was taken off the market and without FDA having to do anything.

Dr. SHUREN. It remained on the market and there was continued use for a while and then use started to dip down. But is that really the system we want, that we have bad tests, people can get hurt by it, and then afterwards if you find the problem and you get on top of it, then something happens to the test? The whole point of premarket review is and why we do that for the other tests—

Mr. BARTON. You are going to guarantee if we would let your agency review all these diagnostic tests, the laboratory tests, that something like that will never happen again, that you all are perfect and all-knowing and you are going to do it in a cost-effective way and it will be peace and light from now until Judgment Day?

Dr. SHUREN. I will not promise you perfection, and I will leave it to God to decide if there will be peace on Earth, but—

Mr. BARTON. Well, I am glad to hear somebody use—

Dr. SHUREN. But that said, we have—

Mr. BARTON [continuing]. The Divinity's name in a positive way. That is—

Dr. SHUREN. Yes, well, they can fire me.

Mr. BARTON. That is a good thing.

Dr. SHUREN. But we have almost 40 years of experience of regulating in vitro diagnostic tests and assuring that those tests are accurate, reliable, and clinically—

Mr. BARTON. I mean, granting your point at least partially, wouldn't it be better to give FDA or some State regulatory agency—it doesn't necessarily have to be Federal—some sort of a penalty assessment that we can immediately put a stop if there is a bad test? Wouldn't that be a better use of your agency's resources? So to use your example, if that were to happen again, boom, we catch it, we stop it, we hit them with a big penalty and get that test off the market. I am not being a horse's rear on this, but, you

know, if it is not broken, don't fix it, and it looks to me like we are just looking for ways to give the CMS and the FDA more authority. And it is obvious that Chairman Pitts and Chairman Upton and I assume Mr. Pallone and Mr. Green are concerned, too. But more regulation is not always the best answer.

I guess my last question would be under the current system what role if any do the States play in looking at these tests?

Dr. SHUREN. So there are States—I can let Dr. Conway talk about it in terms of States that are involved in accreditation of laboratories, but they are not involved in premarket review for those tests with certain exceptions. New York State does do a review of tests. And quite frankly, under the proposal we have, we have the opportunity to leverage third parties. If New York State is meeting appropriate standards, we could leverage some of the work that they are doing.

But I will tell you the problems are more prevalent than people want to recognize. You know, one of the medical centers at the University of Texas was concerned about this—

Mr. BARTON. I went to A&M so that doesn't scare me.

Dr. SHUREN. No, no, no—well—but I will tell you what they were finding is—

Mr. BARTON. I am going to hear it whether I want to or not.

Dr. SHUREN. That is right. Thank you for that. But there were inconsistencies in what they were seeing reported by labs for the same kind of tests, so what they did is they took results from 105 of their cancer patients and they had results from one laboratory, they sent it to a second laboratory, and of the 32 gene variants, they found 50 percent disagreement, 50 percent. And so they even concluded that this suggests physician care would differ based on different interpretations of different companies. And this is not the only report out there, other ones reporting 27 percent finding of incorrect or inaccurate results. This is not uncommon. This goes on.

It is fixable, and it shouldn't be fixed after the fact. Why should our people get hurt, and only when that happens—and if we can find it because we don't have the systems to do that—do we take action. Is that really the kind of health care we want to provide? Do we want to spend money on unnecessary care or do we want to spend it on innovation and assuring those tests work.

Mr. BARTON. Well, I am with you on the innovation part.

Mr. Chairman, you know, the other subcommittee's got the FCC commissioners downstairs, so I am not going to be able to stay, but I appreciate you holding this hearing and thank you for the courtesy of the time.

Mr. PITTS. The Chair thanks the gentleman and now recognizes the ranking member of the full committee, Mr. Pallone, 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

I wanted to ask Dr. Shuren. As you know, various stakeholders have been circulating legislative proposals regarding the regulation of lab-developed tests. Among these various legislative proposals, there seems to be a great deal of variance around moderate-risk tests. Some proposals have suggested that no premarket review is necessary for moderate-risk tests, and one proposal would require

premarket review of moderate-risk tests but would allow such tests to be deemed approved if FDA did not act in a specified time frame.

So I wanted to ask you a couple questions about this. In your testimony you noted an example of a test that is moderate risk would blood glucose strips used by people with diabetes and tests to help doctors diagnose heart failure. Could you discuss what FDA considers to be moderate risk and provide some examples of tests that would be considered moderate risk?

Dr. SHUREN. So other moderate-risk tests would be for diagnosing cystic fibrosis, herpes, heart failure are all moderate-risk tests—

Mr. PALLONE. OK.

Dr. SHUREN [continuing]. That we currently regulate.

Mr. PALLONE. Does the FDA believe that premarket review of moderate-risk tests that there should be, and if so, can you describe when you believe that premarket review of a moderate-risk test would be necessary?

Dr. SHUREN. So we do believe that most moderate-risk tests would be subject to premarket review. That is what we do now, but we do find that there are certain circumstances where we can put other mitigations in place that are good enough and you don't need premarket review. We just did that a little while back for next-generation sequencing platforms, when they are just making tool claims. We just did that for autosomal recessive carrier screening tests. And that is a natural course of action. As the science develops, technology evolves, we can actually change risk classification or what a test will have to do to come on the market. That is hallmarks of a risk-based approach.

We are also very concerned about this deemed-approved approach. It essentially says if we don't make it decision in time, it is approved. So a test goes on the market that may be inaccurate simply because we didn't have enough time to finish up the review or, alternatively, we will not approve it to not let it go on the market. And yet if we had the time to work with the lab, we might get a good test on the market. Either way, bad tests on the market, good tests not going on a market, the loser is patients.

Mr. PALLONE. OK. I think you answered my next question, which would be, you know, the deemed approval if FDA does not act. But let me say, can you comment on whether or not—yes, I think you already talked about the deemed approved. So let me go to another question, Dr. Shuren.

I understand that once the test is approved or cleared by FDA and enters the market, laboratories frequently modify the kits either to expand uses or to make improvements to the way the test is performed. And some stakeholders in the lab community have even suggested that manufacturers rely on laboratories to modify tests in order to expand the uses because it is too costly or burdensome to have a test approved for every use. So do you believe that modifications to LDTs should be subject to premarket requirements, and if so, what types of modifications would FDA want to look at before they are put in place?

Dr. SHUREN. So we think most changes that are made would not be subject to FDA review, and that is actually what occurs now for other IVDs. We would review those changes when there is a new

intended use because it truly is a new test. Even CLIA have used that as a new test. Or if there is a big enough change that when a test is approved would determine what its performance specifications are, if now you make a change and it goes outside the performance specifications, we would review that as well.

Mr. PALLONE. OK.

Dr. SHUREN. But it is those kinds of changes.

Mr. PALLONE. Let me go back. There was other thing that I could have asked you about, these tests are deemed approved if FDA didn't act in a certain time frame. Can you explain whether or not you believe patients, physicians, or payers would know which tests were affirmatively cleared or approved by FDA versus tests that were deemed to be approved? Is there any way that they would know that?

Dr. SHUREN. No. I mean if the test is approved, the test is approved.

Mr. PALLONE. So that is one of the dangers if you will. In other words, you said before that you would be concerned that you might approve something that shouldn't be or not approve something that could be. But the secondary problem is that the user is not going to know.

Dr. SHUREN. That is exactly right.

Mr. PALLONE. All right. Thanks a lot.

Mr. GUTHRIE [presiding]. Thank you. And the gentleman yields back. I now recognize myself for 5 minutes for questions.

Dr. Shuren and Conway, what does premarket review mean in the context of lab-developed tests, or LDTs? And how important is it and who should be responsible for such reviews?

Dr. SHUREN. So our premarket review is to determine if the tests are analytically valid, clinically valid, and they are safe for use under their conditions for use. And it is important to conduct those reviews for moderate- and high-risk tests to make sure they work because doctors and patients rely on those tests to make well-informed healthcare decisions. If they get inaccurate results, they could make the wrong decisions and people get hurt as a result.

Mr. GUTHRIE. Thank you. Dr. Conway?

Dr. CONWAY. I agree with Dr. Shuren. And from the CLIA/CMS perspective, you know, we are really focused on laboratory-by-laboratory post-market review of those laboratory protocols, equipment, training of personnel, et cetera.

Mr. GUTHRIE. OK. Thank you. And I have heard that the same type of diagnostic test that is commonly available as both an LDT and a manufacturer kit that can be purchased by a lab, and tests for melanoma are one example. In other words, I could go to hospital A where they have a lab that developed their own test or, by chance, I could go to hospital B, whose lab purchased a test from a manufacturer. Can either of you walk me through this scenario from a regulatory perspective? In the case of hospital A, is it true that neither FDA nor CMS will have reviewed that test for clinical validity?

Dr. SHUREN. That is true. The test across the street would have been reviewed, and therefore, doctors and patients have the confidence to be able to rely on it, and you don't know in the case of the other one that has been offered.

Mr. GUTHRIE. OK. Same——

Dr. CONWAY. Yes, same. And CMS, once again, would not review clinical validity as part of the CLIA process.

Mr. GUTHRIE. OK. Doing the premarket review of these types of tests, could each of you describe the general education and professional background and expertise of your reviewers?

Dr. SHUREN. So our review, particularly for more complex tests, tends to be performed by a team of experts. They may include physicians, Ph.D. scientists, and statisticians that do a deep dive into the scientific data. We review the science to see if in fact and not only that test works but what it is claiming to do matches up with the science.

Mr. GUTHRIE. Thank you. Dr. Conway?

Dr. CONWAY. Our CLIA team does not include any medical officers or other personnel trained in detailed biostatistics or Ph.D.-level training. Our CLIA team is really focused on, as I mentioned, laboratory assessment on an accreditation and quality and survey and certification framework in a post-market manner laboratory by laboratory.

Mr. GUTHRIE. Thanks. And, Dr. Shuren, you previously testified about challenges you face in hiring and retaining sufficient medical expertise. How would your ability to do so be impacted if CMS were required to have the same types of expertise regarding test design and development?

Dr. SHUREN. Well, first off, I want to thank the committee for trying to take actions in 21st Century Cures to help us to better be able to attract and retain high quality talent. And that is where the answer lies.

Mr. GUTHRIE. So the competition if CMS is doing the same would be——

Dr. SHUREN. Well, it makes no sense for competition, so all we are going to do is create a duplicative system in another agency. I mean it is interesting that people have raised concern about do not have duplicative regulatory frameworks in place, and yet some of the proposals we have seen now to put this under CLIA would do exactly that. It would create all this duplication the right now, as you have heard from both of us, doesn't exist.

Mr. GUTHRIE. All right. Thank you. And I yield back the balance of my time.

And I now recognize Ms. Castor from Florida.

Ms. CASTOR. Thank you, Mr. Chairman. And thank you both for being here today.

As we continue to develop a greater understanding of the genetics of individuals who have a wide variety of diseases and conditions, we are moving away from one-size-fits-all medicine to more targeted and effective prevention strategies and treatments and even cures. This is known as personalized medicine, and I believe it is fundamental to the vision of 21st Century Cures and holds great promise.

This vision, though, will in large part be dependent upon accurate genetic tests, so it is imperative that these tests are scientifically credible. Dr. Shuren, can you provide some examples of the types of genetic tests that are being developed to help deliver per-

sonalized treatment? And describe in greater detail the role that these tests play in precision medicine.

Dr. SHUREN. So increasingly, we are seeing genetic tests being developed to help identify what the appropriate treatment may be for patients who have various conditions, including cancer. And it is critically important that those tests work, because if not, people are not getting the right treatment or they are not getting treatment when in fact they should get treatment.

I will say that as we approach this, though, Government can be innovative. Increasingly, we are seeing next-generation sequencing tests being used, and last December, we put out a proposal for a new approach on next-generation sequencing that, rather than your standard model of maybe doing a clinical study is to leverage data in existing curated databases, which can allow for the clinical community to crowd-source the evidence, and as the science ultimately evolves to where it needs to be to be able to make claims about the use of that test. That way, the regulatory framework can stay step-in-step with the evolution of the science.

In fact, we just held a two-day public meeting last week on this. There is a lot of support for moving forward with this approach. We have even relied on those curated databases to approve a test for cystic fibrosis.

So that is where we need to focus our attention, and that is why we want the lab community at the table with us. Let's focus on the science. That is what we need to do. We have the regulatory tools. It is the science we have got to work together on. And we can do it if people are willing to work with us.

Ms. CASTOR. Yes. And during our 21st Century Cures hearings and briefings, there was a lot of talk about data-sharing. What is going on—because we can't wait for Congress to act, frankly. What is going on with FDA and NIH and a lot of those research institutions across the country in being able to look at that data, share it, so we can develop the cures and treatments of the future?

Dr. SHUREN. Yes. So NIH has its own database of genetic variants. They do an assessment. We have other databases out there. We are now trying to work with these various groups on what the appropriate standards should be for the quality check for the curation and what should be the standards for clinical validity when you are evaluating that science.

Also, we at the FDA have been developing a platform called precision FDA that would allow these test developers to essentially either share their genetic data to compare or providing analytical tools so they can test-drive some of these next-generation sequencing technologies to see if they are accurately sequencing the genome. We think this is a great role, if you will, to provide these common goods to all developers.

Ms. CASTOR. Great. I do, too. Thank you. And I yield back my time.

Mr. GUTHRIE. Thank you very much. The gentleman from Illinois, Mr. Shimkus, is recognized for 5 minutes.

Mr. SHIMKUS. Thank you, Mr. Chairman. And welcome.

Actually, I appreciate the comments from my colleague from Florida. That is kind of where I was just heading to a little bit, too, with the personalized medicine and the genetic testing and really

being accurate on that test so then you can, as we talked about in the other piece of legislation, target based upon the genetic code or the individual patient. That is very exciting.

And the other thing I think we have followed through the hearings and the 21st Century Cures is that then you just don't go down the route of prescribing remedial health action to someone without really full information, so the high cost of health care because you try this, didn't work, try this, didn't work, now you are trying this, and you can get more specific information. So it is very exciting times. And I think people were going around the same issues.

But I wanted to ask this, and it is probably something I should know if I would have more thoroughly read my briefings, but when we talk about risk—basic, moderate, or high—so we are really focusing on moderate and high risk of the tests. What is the risk component? Is the risk component the risk of conducting it, the risk of not having accurate information, or the risk to the patient who hopes to get good information from a test because of the healthcare environment they presently find themselves in? So can you both talk on how do we define risk?

Dr. SHUREN. Yes. So the key consideration is the risk to the patient if they are getting an inaccurate result, they are getting a wrong result, and that is within the context of what would otherwise happen to that patient in clinical care. That is the way we look at it.

Mr. SHIMKUS. So when you use the example of heart, you put that in a moderate—when you were giving the examples of—and I was kind of surprised. I mean, heart disease or heart issues, I think people would find it pretty risky if you have got heart disease, a higher risk than just in the moderate category. So there is some subjectivity to this or—

Dr. SHUREN. Well, so when we look at it, you put it within the clinical context. So in the case of heart failure, when you are making, you know, a diagnosis, there are other things that the clinician takes into account in making that determination. That is a little bit different, though, when I am dealing with something, let's say, like HIV where not only am I dealing with a high-risk condition, right, the risk to the patient is huge, secondly, I don't have another great means of truly determining is that HIV. And then there is also the risk of if I am wrong about this and that person goes out and doesn't know they have HIV, they may engage in activities that they will spread the disease. So we are really looking at it in the practical context of what in fact happens to the patient, not just simply the condition itself.

Mr. SHIMKUS. Right. And I think this is a tough area for conservative Republicans who think Government is too big, costs too much, but there is obviously a position of we want to make sure that people are advertising and using tests, that they are given some stamp of approval, that they meet the requirements and the desires of what they are.

So, Dr. Conway, real quick, you admit that the volume and complexity of these tests have kind of grown, I don't know, I would say exponentially almost. Would you agree with that?

Dr. CONWAY. Yes. We don't have exact numbers for some of the reasons described, but it seems exponential.

Mr. SHIMKUS. But you haven't asked for new authorities because of this growth, have you?

Dr. CONWAY. So CMS has not put forward additional requests for statutory authority. As I mentioned, we think FDA can play a critical role in the premarket review, and we can play a critical role laboratory by laboratory, post-market.

Mr. SHIMKUS. Yes, in your area do you require an individual review of the area that you have been involved with? Is there an independent review process of decisions that you are making, you know, in the CLIA process?

Dr. CONWAY. Let me try to answer that. So I think we have a central office that has oversight of State surveyors, and therefore, oversight of the processes of those State surveyors. We also oversee accrediting organizations, of which there are seven. They have to meet or exceed CLIA standards, and we review that, including if any—

Mr. SHIMKUS. But you are almost evaluating the organizations. The organizations aren't evaluating the independent decisions?

Dr. CONWAY. We have bidirectional communication both with the States and their accrediting organizations like in any of our accrediting organizations, including at times in various programs accrediting organizations identify regulations or standards that need updating.

Mr. SHIMKUS. Great. Thank you very much. I yield back my time.

Mr. GUTHRIE. I thank the gentleman. The time is expired.

And I recognize Dr. Schrader from Oregon for 5 minutes for questions.

Mr. SCHRADER. Thank you, Mr. Chairman. And I would like to thank Dr. Shuren and Dr. Conway for being here. Interesting topic. I would hope that the chair or vice chair and ranking member would hopefully have us have an opportunity to talk to the stakeholders, including the physician groups, just to get a balanced perspective here. This is pretty darn important if we are going to go down this road, and I think the tender of the questions so far indicate that.

And I appreciate the fact both of you testified in total agreement in pretty clear terms about how you guys have two different jobs in the different agencies. It is tough from a practitioner's standpoint, being part of the medical community, to really understand why that has to be. I understand it is right now, but I am not sure why it has to be. It seems odd to me that the Center for Medicare Services—medical services would not have some sort of health regulatory role or clinical analyzation capability.

And it seems to me both of you are going to have to staff up, well, particularly FDA if you take on this new role of premarket approval. There is going to be a huge staffing increase. Why would that not also be possible for the folks in CLIA or somewhere in CMS to do the same thing? I ask both of you that question.

Dr. SHUREN. So we already have existing staff who do exactly these kinds of reviews, and we have years of experience on it. We have training programs for our people. And in terms of additional resources, one of the reasons that we put in place a phased-in ap-

proach would be also for tests that are out there, one, not disrupt the market; two, that we could try to accommodate what resources we have. But in addition, if we need additional resources, we have a user-fee program under which we work with the regulated community about appropriate funding for services that we then provide back like performance and premarket review. And that program, as you know, has been in place for a number of years.

Mr. SCHRADER. So minimal staffing increase is what you are suggesting?

Dr. SHUREN. It depends on the ultimate framework that goes into place as to what that workload would look like.

Mr. SCHRADER. All right. Mr. Conway, if you can.

Dr. CONWAY. On the CMS side, as I mentioned in the central office we have approximately 25 people in total overseeing CLIA. They are trained for their job, which they do well, which is oversight of laboratories, laboratory by laboratory. There are no medical officers, there are no Ph.D.'s, biostatisticians because we do not do premarket review.

Mr. SCHRADER. I just get concerned still—sorry—because both your testimonies talk about accuracy, both of you. You both talk about reliability. And that sounds like overlap to me. So I am just concerned that we don't go down that road. Question on peer-review. I mean a lot of treatments and diagnoses are peer-reviewed in the literature and stuff. Has that occurred at all with laboratory tests? Is there any literature reviewing the efficacy of different laboratory tests?

Dr. SHUREN. In our review of tests we do look at published literature, and in some cases we have relied completely on published literature for certain tests like hemoglobin A1c for diabetes.

This issue about accuracy, our look at it, though, for analytical validity is complementary but it is different. We truly look at is the test itself and what it measures, is it in fact accurate? CMS will look at is that test performed properly to get a result.

Mr. SCHRADER. That is correct. So I guess my underlying concern as a medical professional listening to the testimony is that the consumer, as well as the physician or veterinarian, is not misled by having premarket review. There is going to be some certainty that that test is 100 percent appropriate for them in their situation.

The reason I raised the question about the peer review, I mean, generally, the test from my standpoint is a secondary adjunct to helping establish the diagnosis. You got a lot on clinical sides, you got a lot on knowing your patient, got a lot to, you know, based on the environment they are living in. There are false positives all the time in every single test, false negatives in virtually every single test, whether it is a genetic test or, you know, a simple blood test for goodness sakes. I just don't want the consumer to be misled that by having FDA premarket approval, that that test is going to be 100 percent. I think that is a mistake.

At the end of the day I think it is up to the medical community, the physician to put that one small piece of the puzzle into the, you know, whole diagnostic scheme and come up with whether or not that is actually going to be a valid use of their patient.

I am just very concerned the tone here is that we are going to put certainty into the art of medicine when there is not that much

certainty, and the patient will be misled and frankly lead to greater lawsuits and customers frankly not understanding what medicine is really all about.

Dr. SHUREN. And so the accuracy of that test will also depend on what the use of the test is for. You know, when you deal with riskier conditions or where there are some tests you truly rely on the result of that test. Companion diagnostics, for example, it is the result of that test that will be telling you should they get Zelboraf, you know, for melanoma. And in those cases you want to have a higher accuracy.

You are right, it is not 100 percent, but also what we assure you is that that information is made available to the practitioner like you, and you know that when you get that number for how accurate it is, the result, it is correct. It is the——

Mr. SCHRADER. Well, laboratories have different—laboratory information from one lab to the other is going to be different. I can send the exact same blood sample in to a different laboratory. I can send the genetic code in. You testified a moment ago you are going to get different information back. So the idea that it is going to be dispositive, I would respectfully disagree. And I yield my time.

Mr. GUTHRIE. Thank you. The gentleman's time is expired.

I now recognize Dr. Burgess of Texas for 5 minutes.

Mr. BURGESS. Thank you, Mr. Chairman.

Before I start my time, could I asking for a unanimous consent request?

Mr. GUTHRIE. The gentleman is recognized.

Mr. BURGESS. Ask unanimous consent to enter the statement of the Association for Molecular Pathology into the record. And then a further unanimous consent request for a point of personal privilege, Mr. Chairman.

For the past 7 years I have been joined at these committee hearings by Mr. Paluskiewicz, whose last name is so difficult to pronounce we all know him by J.P. And if I ever seem adequately prepared for these hearings, it is only because I have had J.P. advising me before we come into the hearing room. And so it is with great sadness that I announce that J.P. will be leaving my employment, but he will be joining the committee staff, so he will be here for all to participate and the wondrous things that he has to offer to any committee hearing.

Thank you, Mr. Chairman. Now recognize for questions.

Dr. Conway, so if Dr. Shuren puts his guidance out in January, are you no longer necessary?

Dr. CONWAY. No, sir, and let me explain why. I think there will still be a role for CLIA to assess, and this is a critically important role, that laboratories have the proper equipment, training, protocols, and quality assurance procedures in place, and that laboratory-by-laboratory certification, which a few people have talked about, is a critical role for CLIA.

Mr. BURGESS. But, you know, we have heard several times the FDA is under-resourced, so why shouldn't the resources that are going to CMS just simply go to the FDA?

Dr. CONWAY. So I will speak for CMS. You know, I think in the CLIA oversight framework we are efficiently using both central office resources and relying on States, which was a question earlier,

and their State surveyors, obviously a user-fee funded program based on user fees based on moderate, high complexity, et cetera, and volume. And then we also importantly have nonprofit accrediting organizations that are not Government organizations, that we—seven of them—approve that they meet or exceed CLIA standards. We are using people outside of the Federal Government as well to perform these important functions.

Mr. BURGESS. Dr. Shuren, this question has been posed to you several times in this subcommittee or oversight subcommittees about what is the problem that we are trying to solve? And last night at 7:00 p.m. you put out a report that detailed 20 times where perhaps there were problems with laboratory-developed tests, is that correct?

Dr. SHUREN. Yes.

Mr. BURGESS. And I am sure you would make the further statement that there are more than that, but we have also seen in testimony that what is the total universe of laboratory-developed tests? It is in excess of 11,000, is that correct?

Dr. SHUREN. It is above 11,000.

Mr. BURGESS. So the rate at which you have detected problems would be, if my math is correct, .18 percent, which most things in medicine are hardly that reliable. Is that an unfair statement?

Dr. SHUREN. Yes. Reporting systems—first of all, there is no reporting system on LDTs. You are not monitoring for problems. And so you can't say what the rate is, quite frankly.

Mr. BURGESS. It took you 3 years to provide us with 20. When I asked you in hearings, when we were doing the FDA reauthorization, what is the problem we are trying to solve? So today, now, I have your report, 20 problems that we are trying to solve, and we have got a universe in excess of 11,000 tests.

So let me just ask you this, since you think the risk is there from laboratory-developed tests, is there an FDA-approved kit that has ever had a failure?

Dr. SHUREN. Yes. And the point is the reason we can identify when there are problems and we can deal with it is because we have the systems in place and the maker of the test has implemented systems internally to identify those problems. That is critical. And the work that we are doing doesn't occur right now in CMS. It is not duplicative, and they don't go away.

Remember, if you make a test, if you are a conventional manufacturer, that lab is going to get your test. They still have to perform that test properly, and that is what CMS is overseeing, are the laboratory operations conducted properly.

Mr. BURGESS. My time is limited. So do you envision any lack of access to testing because of the changes that you are proposing in the guidance or the committee is proposing in their legislation?

Dr. SHUREN. So we have tried to—a proposal was put in place so that we would not disrupt the marketplace. Our goal here is to try to assure we do have innovation. We think LDTs are important in health care. There is innovation, but—

Mr. BURGESS. I appreciate the recommendation—

Dr. SHUREN [continuing]. There is no value to patients if the tests in fact don't work. And one of the problems is because we haven't regulated, there has been a disincentive for innovation by

conventional manufacturers. And we have heard from them, particularly the smaller companies are saying they are disadvantaged because they make a test and they go through and they have to demonstrate their test works. And then you can have a lab make the same kind of test go out the door——

Mr. BURGESS. I am going to have to interrupt you because my time is limited.

Just as far as the labs themselves, who do you expect to be more greatly impacted, large labs and large hospitals or smaller rural labs? Is there likely to be a difference in the impact? It is a yes-or-no question.

Dr. SHUREN. The answer is you should regardless be developing the science that your test is validated, whether we review it or not.

Mr. BURGESS. If you don't know whether the answer is yes or no, why wouldn't we want to see an economic impact evaluation such as normally would be required in rulemaking but is not required in guidance?

Dr. SHUREN. Well, just to clarify again, whether we were overseeing them or not, a lab shouldn't be putting any test on the market that they haven't gotten the data to validate. What we are saying is you should have the data and we would look at it before the test went on the market to make sure that that test in fact worked.

Mr. BURGESS. And to the question——

Dr. SHUREN. The tests that wouldn't go on the market are the ones that in fact don't work.

Mr. BURGESS. And to the question of an economic impact statement, as would be required under normal rulemaking processes, why shouldn't the committee or the Congress expect that?

Dr. SHUREN. We are not under rulemaking because we are not imposing new requirements. These requirements already exist under the law. As a matter of policy, we have not actively enforced them. And in places where we put an enforcement discretion policy, we have withdrawn it. We have done that through guidance. It has been the practice all along.

I would say in terms of economic analysis, too, we now have seen the lab community has come forward to say LDTs need to demonstrate analytical and clinical validity. Moderate- and high-risk LDTs need to be subject to premarket review. So those pieces, even the lab community has now said, you know what, that kind of a framework needs to be in place.

Mr. GUTHRIE. The gentleman's time is expired. Would you again, Dr. Burgess, make—you had one unanimous consent request that we did not act on, then you went to a point of personal privilege. Can you make that once again before we move on?

Mr. BURGESS. Yes. It was to add to the record the statement from the Association of Molecular Pathology for the record.

Mr. GUTHRIE. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. GUTHRIE. Thank you.

Mr. BURGESS. Thank you.

Mr. GUTHRIE. The Chair now recognizes Mr. Sarbanes from Maryland for 5 minutes for questions.

Mr. SARBANES. Thank you, Mr. Chairman. I thank the two witnesses for being here.

This is obviously a very important discussion, and I always try to look at these conversations through the eyes of sort of my constituents, people out there, and I have got to believe that if some of them are paying attention to this hearing, they would be scratching their head, the typical patient out there, and saying, you mean these kinds of protections and reviews and guidance and so forth are not already in place?

And I understand that, you know, you start out in a different time period, and you are now trying to sort of update the framework that exists to protect patients out there, and I think the average person would think that this is a very reasonable undertaking on your part. So there is going to have to be some heightened degree of oversight and assurance in this arena.

You have probably touched on all this before I came, but could you just take maybe two or three or four of the main categories of kind of constituencies out there and give me a shorthand on their perspective? What are physicians saying about this conversation? What are patient advocate groups saying? I think I can probably guess. You have alluded to the industry, the lab industry itself, but can you just—and in particular, I guess the physician perspective on it would be helpful to me, but if you can kind of shorthand those different lenses on this discussion.

Dr. SHUREN. We have heard mixed perspectives from the physician community. So oncologists have come out to say, yes, you need oversight, you need FDA oversight. Pathologists have felt that, no, we do not. FDA shouldn't be or should have little role in oversight of LDTs. The patient groups have been supportive of FDA. The consumer groups, payers have been—the medical device industry has been, the laboratory community has been split. Some of the labs have been working and promoting a proposal with FDA oversight, and the others have been proposing a system under CLIA.

Mr. SARBANES. The payers, that is interesting. Can you expand a little bit on that? Is that because they are seeing a lot of costs associated with faulty test results in the use of those?

Dr. CONWAY. Maybe I will start since I am a large payer. It is a challenge in the payer aspect, so including in Medicare and similar and private payers. If the tests haven't gone through that FDA review, then we have a system of local contract medical directors in our national office also, you know, small numbers of people trying to review thousands of tests that either are identified to us or we identify that we need to assess reasonable and necessary for coverage. If there were an FDA review, you could potentially take a whole set of those that have been through FDA review and have those be covered and focus on the ones that are leftover. So this is an issue there.

If you don't mind, on the practicing physician point, I am a practicing physician. I train residents and medical students on weekends as well. You know, you want an assurance as a physician that the test is clinically valid and that the report that says the patient has cancer or genetic disease X is correct. And the patient wants that assurance as well.

Mr. SARBANES. Right.

Mr. GUTHRIE. Thank you. And the gentleman yields back his time.

Mr. Lance of New Jersey is recognized for 5 minutes for questions.

Mr. LANCE. Thank you very much, Mr. Chairman. Good morning to you, gentlemen.

Dr. Conway, it is my understanding that it is the Division of Laboratory Services within the Survey and Certification Group within the Center for Clinical Standards and Quality at CMS that has responsibility for administering the program. How many staff within the division are responsible for inspecting labs and reviewing the tests they performed?

Dr. CONWAY. We have approximately 25 central office staff, and then we have approximately 110 surveyors across the Nation and all the States, so a small number per State.

Mr. LANCE. We have heard that there are tens of thousands of LDTs out there. Do you believe that the division is capable of reviewing all of these LDTs in a timely fashion for clinical validity?

Dr. CONWAY. No, they are not, either in a timely fashion or with the current training of the staff that we have.

Mr. LANCE. And therefore, do you believe that new innovation would be effective, I presume, negatively because of the potential backlog?

Dr. CONWAY. Yes, I would be very concerned about a potential backlog and the impact on innovation.

Mr. LANCE. Dr. Shuren, how would the FDA handle the workload and how would these submissions be based in line, on what priority if this were to be handled by the FDA?

Dr. SHUREN. To handle workload, it is one of the reasons we have put in a phased-in approach over a number of years, and review would occur—be prioritized based upon risk. What we proposed is we would start reviewing higher-risk devices before we would look at—high risk before moving to moderate risk.

Mr. LANCE. And to the best of your ability, how long do you believe it would take to review an LDT, your best estimate, Doctor?

Dr. SHUREN. So for the moderate risk LDTs now, the review times are—total times are a little over 100 days, thereabouts.

Mr. LANCE. Thank you. Thank you, Mr. Chairman. I yield back the balance of my time.

Mr. BURGESS. Would the gentleman yield to me?

Mr. LANCE. I yield to Dr. Burgess.

Mr. BURGESS. Thank you.

Mr. GUTHRIE. Dr. Burgess is recognized.

Mr. BURGESS. On that point, could you state that figure again, the moderate-risk LDTs, 100 days? Is that right?

Dr. SHUREN. No, a little over 100 days.

Mr. BURGESS. So there are 11,000 and some laboratory-developed tests. You said earlier that 50 percent are low risk, so presumably, that leaves 50 percent that are in the moderate- or high-risk category, is that correct?

Dr. SHUREN. Yes, that is correct.

Mr. BURGESS. So extrapolating out the number of days, assuming none of them are high risk, they are all low risk, and that is over 100 days of evaluation at the FDA, I mean that is a phenomenal amount of work that is ahead of you, is it not?

Dr. SHUREN. That is one of the reasons why we have looked at phased-in approach. We have gotten feedback, too, if we should consider any changes and take a different approach for some of the tests that are currently on the market, which we are doing. And we are also having those discussions about funding needs as part of user fee discussions, which are going on right now. They get authorized every 5 years. And that has been the natural course of business.

We have those discussions with regulated industry—the laboratory community is that the table—to then talk about if people want to see a certain performance, what does that look like. We know in some of the proposals people have said for moderate-risk tests could that review time be 75 days? We can have a discussion about what it would take for review in 75 days.

Mr. BURGESS. I will say some of the performance metrics that were introduced after the last FDA reauthorization in 2012, I don't know that we ever got satisfactory answers back to this subcommittee or the Subcommittee on Oversight as to how the performance was on that, but there is a general unease that the FDA is able to perform its function in a timely fashion. During the time that we were doing the hearings for the FDA reauthorization, there was hardly a week that went by that there was not someone in my office with a tale of woe about a drug or device that just seemed to take forever in development and that the FDA would sometimes change the rules as that drug or device went through the development process. What assurance can we give to the laboratory-developed test community that they won't encounter similar problems with your agency going forward?

Dr. SHUREN. Well, our review times have been actually improving under MDUFA III. We are meeting our performance goals, as we committed to do. So we are seeing things move in the right direction. And I don't know what is happening to people coming into your office now. I have heard from other Members that they don't have the parade of people that were coming in several years ago.

And you know when I took over the program several years ago, I was very upfront with this committee and others that there were challenges in the medical device program. We had seen roughly a decade of worsening performance, and we committed to turn that around. We committed to make changes regardless of what happened with MDUFA, and then MDUFA came along to give us additional resources. And we have continued to see improved performance, and we are going to continue to work on it, as we have been doing all along.

Mr. GUTHRIE. Thank you.

Mr. BURGESS. I don't know that I share your enthusiasm. Thank you, Mr. Chairman.

Mr. GUTHRIE. Thank you. The gentleman from New Jersey's time has expired, and recognizing Mr. Cardenas from California for 5 minutes for questions.

Mr. CÁRDENAS. Thank you very much, Mr. Chairman.

My first question is to FDA and CMS. Today in your budgeting, are you being asked to do more with less?

Dr. SHUREN. Yes.

Mr. CÁRDENAS. I am not talking about prospectively. I am talking about in the cycle that you are currently in.

Dr. SHUREN. Yes, and that has been even the cycles before then. We are always asked to do more with less.

Mr. CÁRDENAS. OK.

Dr. CONWAY. Yes. So it is also true for CMS, long history of doing more for less. Thank you for the more with less. Thank you for the question. I mean, I have managed in the delivery system. I have managed in CMS. I have never managed somewhere as hard as this. It is ridiculously harder than running a delivery system. And the reason is the amount of resources for the job. We are deploying lean and other operational techniques to increase our efficiency, learning from manufacturing and health systems, and that is working, but this is a major issue.

Mr. CÁRDENAS. OK. Thank you for clarifying that. I don't think the public understands how taxing it is for our agencies to continue to do more and more and more and try to protect the public and allow the American public to know or feel as though there are protections and the agencies are trying their best to look out for making sure that when they are engaged in something that is a—whether it is FDA-approved or it has gone through review of CMS, et cetera, that they can feel safe.

So thank you for continuing to wade through the struggle of doing more with less and doing your best to keep up with that. I hope that we as the holders of the purse, Congress, will recognize that and realize that we are impeding on the safety of our American citizens when we just say no to a reasonable request of resources and we just say do with what you have and do a better job and just make it happen, easier said than done.

And thank you for clarifying that in the environment that you have been and that this is probably the—I interpret that what you said is this is the most difficult environment for you to do justice to your efforts than any other environment you have been in.

Dr. CONWAY. Yes. And I—

Mr. CÁRDENAS. And understand you are not coming across to me as complaining.

Dr. CONWAY. No.

Mr. CÁRDENAS. I think it is important that you just be honest with us the way you have been. Thank you.

Dr. CONWAY. Yes. No, do you mind if I—

Mr. CÁRDENAS. No, go ahead, please.

Dr. CONWAY. This is the best job I have ever had and the most impactful, which is why I have stayed, but the challenge of managing in the CMS environment with the resources we have for the duty we have for the American people is by far the hardest job I have ever had. And I have led in the private sector, large groups, large budgets. It is nowhere close. This is the most challenging job I have ever had in my life.

Mr. CÁRDENAS. And again, I thank you for welcoming the challenge. It is too bad that we don't lessen that challenge by giving you the resources for you to be more effective without worrying about not being effective in your responsibilities.

My family just got the news recently that my wife and I are going to be grandparents for the first time. And just the other day,

we were invited to my daughter and my son-in-law's house, and they revealed to us it is going to be a boy. And the reason why they found is because my daughter underwent a test that went to a laboratory and the results came back. And one of the things that they could tell her—it wasn't the purpose of the test, but one of the things they could tell her is the gender of the fetus. And so it was a wonderful moment.

However, what if the purpose of that test had been inadvertent, the results had been inadvertent? I think that is really what the focus of today is about. It is about safety of the public. It is about accuracy of what is going on out there. It is about whether or not they are being effective. And unfortunately, for those people who want less Government or no Government, there needs to be oversight from somewhere. I personally prefer that Government be involved in that oversight instead of just turning it completely over to private industries, which happens in some cases.

But my question to you is, going forward, how do we as a country make sure that between CMS, between FDA, what your role can be in making sure that these critical tests, these laboratories are being accurate with the information to the patient, to the actual end-user?

Dr. SHUREN. Well, we have established a task force between FDA and CMS—NIH and CDC are also participating—to assure that we are not duplicating efforts. In fact, we have had conversations with certified laboratories, accrediting lab organizations under CLIA, two State licensure programs, and confirmed we are not duplicating efforts, but we do want to make sure we have good coordination moving forward. And we provide the education and information out for laboratories as well as we progress, so that work is happening in the task force right now.

Dr. CONWAY. I agree.

Mr. CÁRDENAS. Thank you.

Mr. GUTHRIE. They gentleman's time expired. And myself, and I think speaking for the entire subcommittee, we congratulate you on the good news and to your family, the next generation of your family, appreciate that very much.

The Chair now recognizes Dr. Bucshon from Indiana for 5 minutes for questions.

Mr. BUCSHON. Thank you, Mr. Chairman.

Now, I have heard complaints that the FDA oversight of LDTs would interfere with the practice of medicine. I am a physician, cardiovascular surgeon, so I would like you both to comment as regulators but also as physicians on your view on that.

Dr. SHUREN. So we do not—and as a physician, we do not regulate the practice of medicine. Congress actually put in a statutory provision prohibiting us from regulating the practice of medicine in the medical device program. It is a unique provision that pertains to us. What we are regulating, talking about regulating, are the tests, the things that we regulate already today, reagents, the instruments, the protocol, instructions are used that go forward with it.

In fact, a group of laboratories who were working with the device industry, the conventional IVD makers, when they sat down and went through it, they began to realize, too, you know what, there

are parts here that is just like what happens in FDA: development, design, validation of tests. Then there are all these other activities that occur that are lab operations or the practice of medicine. They are not under our preview and we have never proposed to ever regulate those.

Dr. CONWAY. And likewise, CLIA does not regulate the practice of medicine. It does regulate laboratories in terms of equipment, personnel, protocols, et cetera, which its focus is post-market laboratory by laboratory.

Mr. BUCSHON. OK. Great. And currently, CMS regulates how physicians operates a lab, as you described, and performs tests within it, but I really haven't heard any complaints about interfering with the practice of medicine myself from people that I know. Why is it that physicians feel differently maybe about the FDA oversight of these particular tests, and how can we address those concerns? Does that make sense?

Dr. SHUREN. It does. I think what we are dealing with are people who haven't dealt with us necessarily beforehand, and so it is new and they are assuming things that we don't believe to be the case. I hearken back to Dr. Burgess, who I respect very much, when he said when CLIA came in the door you were not a fan, but you began to realize the value of it. I would say the same thing here. As the lab community works with us—well, maybe you will allow it.

Well, hopefully, we will see much the same here with the lab community in working with us. And it is our hope they will work with us to make sure that when we are doing things, it also best fits for their operations. Again, we both are committed and care about that those tests work.

Mr. BUCSHON. Yes. I mean I will just make a comment and I will—I mean, as a physician, obviously I want accuracy and patient safety to be at the top of the list, right? And again, I think Mr. Shimkus said I am not one that is generally for Government regulation, but I think in this area that, you know, this is a good discussion to be having on behalf of patients, and that I think the details and how things end up at the end are what are important. So I commend your hard work on trying to find the sweet spot as you go about your job.

Thank you. I yield back.

Mr. BURGESS [presiding]. The Chair thanks the gentleman. The gentleman yields back.

The Chair recognizes the gentleman from Florida, Mr. Bilirakis, 5 minutes for questions, please.

Mr. BILIRAKIS. Thank you, Mr. Chairman. I appreciate it. And this question is for the panel.

As we go forward with any new regulation—regulatory scheme—we need to balance the needs between consistency, accuracy, and innovation. In disease areas such as cancer, genetic testing is evolving rapidly, and I am sure you agree with that. Many major institutions today have developed their own gene panels that help diagnose or identify potential treatments for cancer patients.

For example, in Tampa we have the Moffitt Cancer Center, the only NCI-designated Comprehensive Cancer Center in Florida. They have developed a TruSight Tumor Gene Set, which is used to

identify lung and colon cancers that will benefit from targeted therapies. An advantage of the lab-developed tests is the ability to rapidly innovate current tests rather than the slower and expensive process of resubmitting to FDA for any changes. Centers such as Moffitt have the ability to innovate and rapidly improve their lab tests as fast as science evolves.

Question: How can we resolve issues regarding consistency and accuracy and not stifle innovation in these labs and important healthcare institutions?

Dr. SHUREN. So one issue for consistency, certainly we don't—we were recommending not to have two duplicative systems out there, one under FDA, one under CMS, or we will have inconsistency. But then we have found that to assure consistency, we work with the community on trying to develop standards or in guidance so that, as we learn and the science evolves, we can have more of a common playing field of what performance should look like for certain kinds of tests. And that can help ensure consistency in terms of approach.

Mr. BILIRAKIS. Thank you. Anyone else?

Dr. CONWAY. I agree with Dr. Shuren, and I think, you know, from the CMS perspective, we think our strength is in that post-market review laboratory by laboratory on the qualifications, equipment, and personnel.

Mr. BILIRAKIS. Thank you. Anyone else want to jump in? OK. Dr. Conway, since both the volume and complexity of lab-developed tests on the market today have drastically increased in recent years, why hasn't CMS asked for these new authorities?

Dr. CONWAY. So in terms of authorities we think FDA has a critical role in premarket review of clinical validity. We think CMS's role through CLIA really is and should be focused on laboratory-by-laboratory assessment, survey and certification and oversight of accrediting organizations, ensuring that the protocols, the equipment, and the standards are in place in individual laboratories in a post-market manner.

Mr. BILIRAKIS. Dr. Conway, does CMS require definitive review of the clinical claims being made about the tests?

Dr. CONWAY. And Dr. Shuren can certainly comment for FDA. On the CMS perspective, we do basic assessment of analytical validity so the analyte is the actual analyte in the test. We do not do assessments of clinical validity, meaning the test actually identifies the condition, the absence or presence of the condition it is supposed to identify.

In our coverage process, we have occasionally looked at laboratory development tests for reasonable and necessary standard. There, we will look at the effect of the test on patients, but that is a very small number of LDTs we have looked at through that process.

Mr. BILIRAKIS. Well, thank you very much, and I yield back, Mr. Chairman.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back.

The Chair recognizes the gentleman from New York, Mr. Collins, 5 minutes for your questions, please.

Mr. COLLINS. Thank you, Mr. Chairman.

Before I start my questions, I would ask unanimous consent to enter into the record a letter from Roswell Park Cancer Institute.

Mr. BURGESS. Without objection.

[The information appears at the conclusion of the hearing.]

Mr. COLLINS. Thank you very much.

In that letter they do mention the same we have talked about before, the Association of Molecular Pathology, or AMP, and their proposal, and I would certainly encourage the FDA, as we are in the discussion stage, to again take a look at this.

So I guess one thing I am still trying to get clear on, you know, currently, a commercial test, something sold on the market which does have to go through FDA approval, premarket approval, and I assuming that is currently a 510(k)?

Dr. SHUREN. For premarket, most of them are 510(k). A very tiny number are PMA.

Mr. COLLINS. So as a 510(k) currently, it is a medical device subject to the medical device tax, correct?

Dr. SHUREN. Yes.

Mr. COLLINS. So if I understand what your guidance is now, you are going to move on IVDs out of that world, the medical device world, and have a different classification of class 1, 2, or 3, or low, moderate, whatever. Just a question, does that mean on the good news side that IVDs will no longer be subject to the medical device tax since they are not going to be getting 510(k)s?

Dr. SHUREN. So the trigger for the device tax is registering at the listing with the FDA. What we have proposed for LDTs is that—and we use that to know what test is being made, who is making it, and that is a requirement by law. But we have worked through that instead they can give us a notification and not list with us, and particularly—and that is for starters. And for the tests that don't ultimately come in for premarket review, they also wouldn't end up registering and listing with us. And that would not trigger the device tax.

Mr. COLLINS. So current tests would be still covered by the medical device tax even though there is not a 510(k) because they would be listed with the FDA?

Dr. SHUREN. They are registered and listed with that, and those are—

Mr. COLLINS. OK. That clarification is important because I have heard that kind of going all over the board.

Now, another, you know, concern has been, you know, accuracy of testing, and I think it is also important to make clear laboratory-developed tests are not sold to other facilities. They are used inside a facility such as Roswell Park, which is looking at very specific treatments for specific cancers and what we call personalized medicine. They are not then selling those tests to other folks or making claims, which is different than a commercialized test, which currently goes through FDA approvals.

But, you know, Dr. Conway, it is my understanding that over 97 percent of the CLIA laboratory test facilities have subjected themselves to outside third-party proficiency testing of their tests. Isn't that correct?

Dr. CONWAY. So proficiency testing occurs in just 13 specialty areas, occurs approximately three times per year. It has improved

the accuracy over time. It will not assess for clinical validity of the test, so the premarket clinical validity, which Dr. Shuren spoke to, the proficiency testing does not analyze clinical validity.

Mr. COLLINS. Well, it certainly analyzes whether you are properly getting—you know, you are identifying the antigen you are supposed to identify.

Dr. CONWAY. So it will identify—if that laboratory-developed test was within those 13 categories, which they are not all within those 13 areas, but for an LDT that was in one of those 13 areas—and Dr. Shuren may say more—it will detect that the analyte is the analyte, but that is not an assessment of the clinical usefulness or validity of the test.

Dr. SHUREN. And it goes to again, if you will, the accuracy of the performance of the test as opposed to the accuracy of the test itself, which is a different look, and that is what we look at for the test.

Mr. COLLINS. Yes. I guess I would just say it is my belief anyway that the laboratory-developed tests, certainly in institutions like Roswell Park, are being done to get better treatment, quicker treatment to the patients. And a big concern all of us have, if this goes through, that a test might be used tomorrow to help a patient with cancer now is delayed 6 months as it goes through some kind of premarket review at FDA, which is a life-and-death situation for many of these cancers.

And I think it goes back to—I think I go on to the same bandwagon as Mr. Barton and Dr. Burgess. This has not been a problem that I would identify, and putting any type of delay into this sphere of personalized medicine and treatment especially in the cancer and oncology world runs the risk frankly of causing people to die that don't need to die, treatments that could be given that would be delayed. And in the cancer world, delay is not a good thing.

So personally, I would throw myself into the category I believe it is working now. We do have outside proficiency testing, third-party testing. And we have to remember these are laboratory-developed tests that are not being sold in the marketplace to other facilities, which is very different than what you are doing now.

My time has expired, but if the Chair would like to hear a response, I would certainly yield a couple seconds.

Mr. BURGESS. Sure. He is recognized for a response.

Dr. SHUREN. I truly appreciate those comments because we do not want to stifle innovation in this place. We want to have patients get timely access to tests. And that is why even under an FDA mechanism if the test is being reviewed, it is being developed, it can still be made available to patients on an investigational basis or for compassionate use. But there at least you are telling the doctor and you are telling the patient we haven't validated this test yet. It is investigational. This may be—

Mr. COLLINS. You know what, I appreciate that because my worry was they would develop a test, they couldn't use it until they had approval, but if on an investigative basis they know that—they think they have a good test they can use it, then you have actually helped me in a couple of ways there. Thank you for that response.

I yield back.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back.

The Chair recognizes the gentleman from Pennsylvania, Mr. Murphy, 5 questions for questions, please.

Mr. MURPHY. Thank you. Doctor, Doctor, it good to have you here, appreciate this.

I want to pivot a little bit here to talk about piecing together post-market and premarket analysis to look at this, and in particular, a couple of devices used in women's health care, one is called a morcellator. Are you familiar with the morcellator, a device that is supposed to shred tumors, et cetera, but has been associated with complications in women in terms of actually spreading cancer for them?

Now, it has been on the market for 20-plus years, and the FDA admitted for the first time it became aware of the safety issue with power morcellators was after December of 2013, correspondence from a physician citing the case of a family member. This is someone who had just recently had another surgery to remove another recurrence of cancer that was spread it by the morcellator.

The manufacturer was apparently aware of the dangers of this device as early as 2006 based upon a report from Dr. Lamparter, a pathologist from central Pennsylvania, who cited about 1 out of 300 samples of morcellated tissue from his hospital had evidence of a hidden cancer, which is morcellated.

So my question is did the FDA have any evidence of these dangers in 2006 or prior to that? Are you aware of this problem?

Dr. SHUREN. So in the past the thought was what risks of cancer there may be for a fibroma—for a fibroid actually to have cancer in there—were significantly less. And one of the things when we looked into it more recently we came to a different conclusion, that the likelihood of cancer is higher. There is still disagreement in the community because, as you know, the healthcare professional societies disagree. They think we have overestimated the risk of cancer.

We said we have a different perspective, and that is why we went out and we put contraindications and warnings on the use of that device, that it should only be used in a more limited set or offered as an option in a limited set of women and think about primarily women who, in the absence of using the device, would no longer be able to bear children but they want to bear children. And we felt those cases the risk of the cancer is very low. They should have the opportunity to weigh in, but we scaled back dramatically how that should—

Mr. MURPHY. So this is a case where the science available, the premarket analysis has changed, and what is being used in the data, you have a mechanism to go forward on this and make some changes. Let me ask another question.

Brigham and Women's Hospital was aware of the dangers in 2012. A patient by the name of Mrs. Erica Katz was seriously injured in 2012 by the device and then died in 2013 according to reports. I wondered, do you know if that hospital reported that to the FDA? Would you know?

Dr. SHUREN. I am not aware that—

Mr. MURPHY. Is there a mechanism where the hospital is supposed to report that or the manufacturer is supposed to report that so you can do the analysis?

Dr. SHUREN. So user facilities have certain requirements for reporting. So do manufacturers if they become aware of certain events. And what I can tell you is we have been looking into those concerns that have been raised regarding reporting.

Mr. MURPHY. OK. In response to congressional inquiries about this, the FDA admitted that the 1-out-of-350 risk does not address other types of malignancies, which you would add to that risk, you said. They went on to say the FDA also identified studies showing that morcellated patients had worse outcomes than patients who had not undergone morcellation.

So this is more than just the issue with just a fibroid or if it is cancerous. It is also a question of outcomes. Is this something that the FDA is reviewing also with regard to their stamp of approval on these things in terms of the outcome measures?

Dr. SHUREN. So in terms of the tests we have looked at, we think where we have constrained it right now is—for use is where the benefits outweigh the risks, but we are continuing to look at new data as it arises, and if so, we will act accordingly.

Mr. MURPHY. Thank you. There is another issue in women's health that was brought to my attention. It is a product called Essure. It is a permanent birth control device that went through FDA's rigorous premarket approval process. Yet despite getting the agency's approval, it has been linked to at least four deaths and deaths of five unborn children. Apparently, a total of 24,000 women have come forward claiming that they have been harmed by this device. And so the question is how it remains on the market with a potential for problems. And because this has the FDA stamp of approval, these women feel at this point they cannot take their cases forward, and they feel they don't have any recourse. Is the FDA also reviewing this issue as well as far as you know?

Dr. SHUREN. We are. In fact, we held an advisory committee meeting a few weeks ago at our behest to give an opportunity to put what new evidence is on the table to assure that people who wanted to raise concerns about it had an opportunity to provide those concerns. And we are now currently reviewing the feedback we received from the advisory committee, as well as what we have heard from other people, as well as the state of the evidence, and we will come out with our conclusions on that to the public.

Mr. MURPHY. Thank you. And as this goes through, since this hearing has been a lot about premarket analysis, what this comes down to is I just want to make sure that we are aware of what mechanism you have, because I understand the science of 1996 is different from the science of 2015 and our knowledge base, but to have an ongoing mechanism for review and changes, devices and getting information there and looking at those things, I mean, I am glad you had some hearings on this, but I would certainly like to know that that is part of the system.

I am out of time, but I look forward to hearing your comments on that in the future. Thank you.

Mr. BURGESS. The gentleman yields back. The Chair thanks the gentleman.

The Chair recognizes the gentleman from Texas for a unanimous consent request.

Mr. GREEN. Mr. Chairman, I ask unanimous consent to place in the record “Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies.” I ask unanimous consent to place that in the record.

Mr. BURGESS. Without objection, so ordered.¹

Mr. BURGESS. And I recognize myself for an additional unanimous consent request to add the statement of the American Association of Clinical Chemistry to the record. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. BURGESS. Seeing no further Members wishing to be recognized for questions, I do want to remind Members they have 10 business days to submit questions for the record, and I ask the witnesses to respond to those questions promptly. Members should submit their questions by the close of business on December 2.

With that, the subcommittee stands in adjournment.

Dr. SHUREN. Thank you.

[Whereupon, at 12:07 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

PREPARED STATEMENT OF HON. FRED UPTON

The 21st Century Cures Act passed this committee 51–0 and was through the House in July with 344 votes. It was the product of over a year’s worth of ideas Members received at hearings, roundtables in DC and across the country. Provisions were proposed and fleshed out with the help of a wide variety of stakeholders, in and out of Government, of all political stripes. It goes without saying that for any piece of comprehensive legislation to garner these vote totals, compromise is critical and the perfect can’t become the enemy of the good. It also goes without saying that some important pieces of the puzzle didn’t get included because the timing just wasn’t right. Modernizing our regulatory framework for the review and oversight of diagnostics is one of those pieces.

As I said at our first forum on this topic in July 2014, these increasingly important and complex tests are providing researchers and clinicians with valuable tools to match the right patients with the right treatments. We must ensure that our laws and regulations keep pace so that innovation in this space continues and patients benefit from accurate and reliable tests.

I saw Cures as a unique opportunity to elicit feedback on what such a framework should look like and what role Congress could play in developing it. We issued a white paper asking targeted questions and were overwhelmed with the scope and thoroughness of the responses we received. We realized early on that the traditional medical device framework was not ideally suited for these unique tests, which provide clinicians with critical information but do not actually provide therapy to a patient.

It was also apparent that there was quite a difference of opinion about what the roles and responsibilities of FDA and CMS should be. Developing legislative language with broad support on an abbreviated timeframe was not achievable. I told my staff to table these discussions until we got Cures through the House but to urge stakeholders to use the time to forge ahead and find as much common ground as possible.

I was very encouraged to hear that a diverse group of stakeholders with different points of view came together and, in the spirit of finding consensus, developed a draft framework that answered a lot of our questions in a responsible, balanced manner. Of course there is room for improvement, but folks need to be realistic in their approach and pragmatic with their suggestions if the ultimate goal is a bill signed into law any time soon. We must get this right and we need everyone’s help in order to do so.

¹The information has been retained in committee files and also is available at <http://docs.house.gov/meetings/IF/IF14/20151117/104127/HMTG-114-IF14-20151117-SD009>.

PREPARED STATEMENT OF HON. RENEE L. ELLMERS

Earlier this year, Democrats and Republicans on the House Energy and Commerce Committee worked together to develop the 21st Century Cures legislation. I was proud to work with my colleagues on that landmark initiative in order to reduce regulation, inspire innovation, improve outcomes for patients and move our country towards precision medicine. Further, that legislation helped highlight the increased importance of diagnostics in modern health care.

Today, diagnostics play a critical role in the rapid detection and diagnosis of diseases. Diagnostics help identify targeted, effective and often less invasive treatments—ultimately leading to reduced costs to both patients and the Government.

The Committee's current discussion draft legislation follows the work of 21st Century Cures and focuses on the future of diagnostics. It would advance innovation, protect patients, provide a predictable and timely path to market and avoid duplicative regulation. It does this by tailoring an appropriate role for the FDA (outside of the medical device framework) to oversee diagnostic test development activities, while modernizing CLIA oversight of separate and distinct laboratory operation activities.

Without this legislation, I am concerned that the FDA would finalize guidance to regulate laboratory developed tests as medical devices, which could impact many stakeholders. This guidance may lead to costly litigation and uncertainty or could hamper innovation and patient access to critical diagnostic tests.

Also, I am deeply concerned that this guidance would result in the medical device tax being imposed on laboratories. Dr. Shuren confirmed during the hearing in September 2014, that under the FDA's guidance, labs would ultimately be directly subject to this medical device tax. Labs already pay the tax indirectly when they purchase test kits from manufacturers, so under the guidance they would unfairly pay the same tax twice.

I have many stakeholders in my district, so this discussion draft legislation represents a good compromise between the CLIA-centric approach and the medical device framework laid out in the FDA guidance. In addition, my district is home to many veterans and military families who rely on TRICARE for their health care, so ensuring market stability and access to these crucial tests directly affects my constituents.

I am thankful for stakeholder engagement in finding a legislative solution that provides a feasible alternative to FDA's draft guidance. I stand prepared to work with the chairman and ranking member in order to accomplish this goal.

November 16, 2015

The Honorable Lamar Alexander
Chairman, Senate Committee on
Health, Education, Labor and Pensions
428 Senate Dirksen Office Building
Washington, DC 20510

The Honorable Fred Upton
Chairman, House Committee on
Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Patty Murray
Ranking Member, Senate Committee on
Health, Education, Labor and Pensions
428 Senate Dirksen Office Building
Washington, DC 20510

The Honorable Frank Pallone
Ranking Member, House Committee on
Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Dear Senators Alexander and Murray, and Representatives Upton and Pallone:

On behalf of the undersigned organizations and laboratory directors, we are writing to urge Congress to enact legislation to modernize the laws that enable oversight of clinical laboratory diagnostics, including laboratory developed test (LDTs) services and *in vitro* diagnostic (IVD) test kits. Both the Senate Committee on Health, Education, Labor and Pension (HELP) and the House Committee on Energy and Commerce (E&C) have demonstrated dedicated leadership on the critical issue of clinical laboratory diagnostics through extensive stakeholder engagement. We believe your leadership has created the opportunity to enact legislation to ensure our nation's patients continue to have robust access to innovative and high quality clinical laboratory diagnostics.

As you are aware, clinical laboratory diagnostics are a vital component of health care impacting the overwhelming majority of patients across the country. Every day, laboratory physicians and practitioners employ innovative diagnostic technologies, methods, and knowledge to deliver critical and life-saving clinical information to assist physicians and patients in diagnosing, assessing, preventing and treating diseases and conditions. The unlocking of the human genome has allowed diagnostic innovation to boom over the past two decades leading to precision medicine tests with higher accuracy, precision, and predictive ability.

These more specific and personalized diagnostics allow for earlier and in many cases preventive clinical interventions which ultimately reduce the cost of care, increase the patient's quality of care, and can save lives. Whether in the context of 21st Century Cures, Innovation for Healthier Americans, or the President's own Precision Medicine Initiative, the furtherance of innovation in clinical laboratory diagnostics is vital to our shared goals of bending the cost curve in health care and a healthier America.

These goals, however, are in danger as innovation is far outpacing federal regulations based on statutes that in the case of FDA are nearly four decades old, and in the case of CLIA are almost three decades old. These statutes were enacted at a time when the rapid advances in

personalized medicine, and critical importance of advanced diagnostic tests could not have been foreseen. The 2014 FDA draft guidance documents proposing to regulate LDTs as medical devices show the problematic limits of current oversight. The guidance proposals threaten both current access to, and the future development of, tests that impact the care of all Americans. We believe that allowing FDA to move forward with finalizing the draft guidance documents is the wrong approach and legislation is needed in lieu of the FDA guidance.

The ensuing conflict between innovation and access on one side and the need for oversight on the other has led to numerous proposals for reform over the past year. The proposals vary in approach and breadth, but collectively they prove that the underlying statutes are deeply in need of modernization through Congressional action.

We, the undersigned, believe that with your help and leadership, stakeholders can reach consensus on a modernized statutory framework to oversee clinical laboratory diagnostics that ensures patients have access to innovative and high quality diagnostic services. We urge you and the rest of your colleagues in Congress to advance reform legislation; we pledge to work with Congress and the Administration to achieve enactment.

Sincerely,

Organizations & Stakeholder Groups

American Clinical Laboratory Association
California Clinical Laboratory Association
Coalition for 21st Century Medicine

Laboratory Directors

Edward R. Ashwood, MD, Associate Vice President for Government Relations/ARUP, University of Utah

Robert W. Allan, MD, Professor of Pathology, Medical Director, UF Health Pathology Laboratories, University of Florida

David F Keren MD, Professor of Pathology, Director. Clinical Pathology, The University of Michigan, Ann Arbor Michigan

Daniel A. Arber, MD, Interim Vice Chair, Clinical Pathology, Stanford University

Jerry W. Hussong, MD, Chief Medical Officer/Director of Laboratories, ARUP Laboratories, Senior Vice President, ARUP Laboratories, Director of Hematologic Flow Cytometry, ARUP Laboratories, Professor of Pathology, University of Utah

Ronald W. McLawhon, M.D., Ph.D., Director, Clinical Laboratories and the Center for Advanced Laboratory Medicine, Professor of Pathology and Head, Division of Laboratory and Genomic Medicine, Vice Chair, Business Development, University of California, San Diego, School of Medicine and UC San Diego Health

Irving Nachamkin, DrPH, MPH, D(ABMM), FAAM, FIDSA Professor and Director Division of Laboratory Medicine Dept. of Pathology and Laboratory Medicine Perelman School of Medicine at the University of Pennsylvania

Frederick S. Nolte, Ph.D., D(ABMM), F(AAM), Professor, Pathology and Laboratory Medicine, Vice-Chair, Laboratory Medicine, Director, Clinical Laboratories, Medical University of South Carolina

James C Ritchie, Ph.D., DABCC, FACB, Medical Director, Emory Medical Laboratories, Professor, Pathology & Laboratory Medicine, Emory University

Ron Lepoff, MD, Clinical Laboratory Medical Director, University of Colorado School of Medicine, Professor of Pathology, University of Colorado School of Medicine

Curt Hanson, MD, Chief Medical Officer, Mayo Medical Laboratories, Professor of Laboratory Medicine and Pathology, Mayo Clinic

November 11th, 2015

Congressman Fred Upton
Chairman
House Energy and Commerce Committee
2183 Rayburn House Office Building
Washington, DC 20510

Congressman Frank Pallone
Ranking Member
House Energy and Commerce Committee
237 Cannon House Office Building
Washington, DC 20510

Senator Lamar Alexander
Chairman
Senate HELP Committee
SD-428 Dirksen Senate Office Building
Washington, DC 20510-6300

Senator Patty Murray
Ranking Member
Senate HELP Committee
SD-428 Dirksen Senate Office Building
Washington, DC 20510-6300

Dear Chairman Upton, Chairman Alexander, Ranking Member Pallone and Ranking Member Murray:

In anticipation of next week's House Energy and Commerce Committee hearing entitled "Examining the Regulation of Diagnostic Tests and Laboratory Operations," the undersigned organizations, representing patients, advocates, caregivers and health care professionals, would like to emphasize the important role FDA can and needs to play in the regulation of laboratory developed tests (LDTs).

Concerns have been raised that FDA involvement in LDT regulation will impede patient access to innovative tests. However, it is important to note that the FDA has a track record of exercising regulatory flexibility to bring new technologies to patients in a timely manner. For example, in 2013 FDA allowed marketing of four next-generation sequencing (NGS) diagnostic devices, the first-ever clearance of its kind. The FDA developed the expertise and tools to conduct a thorough review and used separate approval pathways to reflect the risk associated with each device. The FDA's draft guidance on LDT oversight also reflects a commitment to flexibility, given the proposal's risk-based approach to oversight.

Beyond providing timely access to new products, the FDA can effectively fill current gaps in oversight that have led to uncertainty surrounding the quality of some tests. The discovery of faulty and clinically invalid tests being used in ovarian cancer (OvaSure) and cardiology (KIF6 testing) highlights examples of inadequate oversight. Apart from these examples, the general lack of publicly-available information about many LDTs has raised concerns among many that not enough is known about many tests currently in use.

As Congress weighs various proposals to reform LDT oversight, we urge lawmakers to recognize that FDA involvement does not mean a threat to patient access. Moreover, patients deserve to have confidence in the results of *in vitro* diagnostic tests, since such tests inform a variety of treatment decisions. The FDA can provide the assurance that when tests are performed they lead to the proper use of associated treatments, a step that's necessary to improve the public health.

Sincerely,

Action to Cure Kidney Cancer	Friends of Cancer Research
Addario Lung Cancer Foundation	Kidney Cancer Association
Addario Lung Cancer Medical Institute	Kids v. Cancer
The ALS Association	The Leukemia & Lymphoma Society
Alliance for Aging Research	Lung Cancer Alliance
American Association for Cancer Research (AACR)	LUNGevery
American Autoimmune Related Diseases Association	Lupus and Allied Diseases Association, Inc.
American Brain Tumor Association	Melanoma Research Alliance
American Cancer Society Cancer Action Network	MRSA Survivors Network
American Heart Association	National Brain Tumor Society
American Medical Student Association	National Coalition for Cancer Survivorship
American Society of Clinical Oncology (ASCO)	National Consumers League
Annie Appleseed Project	National Multiple Sclerosis Society
Breast Cancer Action	National Organization for Women (NOW)
CancerCare	National Patient Advocate Foundation
Cancer Prevention and Treatment Fund	National Physicians Alliance
Cancer Support Community	Ovarian Cancer National Alliance
C-Change	Prevent Cancer Foundation
Connecticut Center for Patient Safety	US Pain Foundation
Cutaneous Lymphoma Foundation	WomenHeart: The National Coalition for Women with Heart Disease
Fight Colorectal Cancer	Woody Matters



**American Cancer Society
Cancer Action Network**
555 11th Street, NW
Suite 300
Washington, DC 20004
202.661.5700
www.acscan.org

November 16, 2015

The Honorable Fred Upton
Chairman
Energy and Commerce Committee
U.S. House of Representatives
Washington, DC 20515

The Honorable Frank Pallone, Jr.
Ranking Member
Energy and Commerce Committee
U.S. House of Representatives
Washington, DC 20515

Re: Examining the Regulation of Diagnostic Tests and Laboratory Operations

Dear Chairman Upton and Representative Pallone:

The American Cancer Society Cancer Action Network (ACS CAN) is pleased to offer comments on the Energy and Commerce Committee's discussion draft legislation updating oversight for all diagnostic tests regardless of origin, including laboratory developed tests (LDTs). ACS CAN is the nonprofit, nonpartisan advocacy affiliate of the American Cancer Society, supporting evidence-based policy and legislative solutions designed to eliminate cancer as a major health problem. Our organizations have a critical interest in ensuring that patients and their physicians have access to accurate information to make decisions about their cancer treatment. We appreciate the Committee's continued work and due diligence to address issues important to cancer patients.

The recommendations included in this letter build upon the comments ACS CAN provided to the committee in January on general oversight parameters for LDTs as well as the more detailed comments we provided in June on a draft version of legislation.

As you know, cancer is literally hundreds of different related diseases that share common hallmarks, but are treated in very different ways. Therefore, the ability to accurately diagnose the type of cancer and to identify a tumor's particular molecular characteristics is absolutely critical in optimizing each patient's treatment. The current regulatory paradigm for diagnostic tests includes two different oversight systems. Tests that are sold as complete kits are required to undergo pre-market clearance and approval from the FDA to verify analytical and clinical validity of the test. Similar tests that laboratories create for their own internal use (LDTs) are not subject to the same level of review even if they purport to perform the same function as FDA-approved kits. It is paramount that patients and their physicians know that regardless of how or where a test is manufactured or performed, they can trust the information produced by that test.

While we support the Committee's desire to harmonize the oversight of diagnostic tests regardless of where they are created and conducted, and calibrating the level of oversight to a

test's risk, we have concerns about many of the details of the current draft legislation. First, we remain concerned that the risk classification proposed in this legislation still does not fully take into account risk to a patient's health, but rather incorporates aspects of technology in defining whether a test is high, moderate, or low risk. Secondly, this legislation still contemplates grandfathering tests developed prior to enactment of the bill, which would leave potentially dangerous tests without adequate oversight. Lastly, the legislation contains provisions that would "deem" a test approved if its application was not acted upon quickly enough by FDA.

We are gratified to see that the discussion draft recognizes that FDA is the most appropriate agency to evaluate the analytical and clinical validity of diagnostic tests along with their safety. We do not, however, believe that the creation of a new Center at FDA is necessary, and it could be potentially burdensome on the agency. We believe that the FDA currently has all the authority, expertise, and regulatory infrastructure necessary to oversee diagnostic tests. As we have stated previously, we support the FDA's October 2014 proposal to begin actively overseeing LDTs under a risk-based framework.

We look forward to continuing the discussion, and being of assistance in creating a final legislative product that meets the needs of cancer patients, survivors, and those who are helping them in the fight against the disease.

Thank you again for the opportunity to comment on this proposal. Please do not hesitate to contact me (Dick.Woodruff@cancer.org) or Mark Fleury (Mark.Fleury@cancer.org) if you have any questions.

Sincerely,

A solid black rectangular box used to redact the signature of Dick Woodruff.

Dick Woodruff
Vice President, Federal Relations
American Cancer Society Cancer Action Network



ASSOCIATION
FOR MOLECULAR
PATHOLOGY

ASSOCIATION FOR MOLECULAR PATHOLOGY

Education. Innovation & Improved Patient Care. Advocacy.
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United States House of Representatives
Committee on Energy and Commerce, Subcommittee on Health

Hearing on

“Examining the Regulation of Diagnostic Tests and Laboratory Operations”

Written testimony submitted by
Association for Molecular Pathology

November 17, 2015

Chairman Upton and Ranking Member Pallone:

Thank you for the opportunity to submit written testimony to the hearing on “Examining the Regulation of Diagnostic Tests and Laboratory Operations.” We appreciate the time and effort that you, the rest of the Energy and Commerce Committee, and your staff have devoted to this important issue, and we strongly encourage the Committee to continue working with molecular pathology professionals as you consider legislation.

The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,300 physicians, doctoral scientists, and medical technologists who develop, perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the government, academic medicine, clinical testing laboratories, and the in vitro diagnostics industry. It is our goal as an organization to ensure that patients have access to innovative and accurate laboratory testing procedures.

Molecular pathology professionals dedicate their careers to ensuring that patients receive the most appropriate services for their clinical conditions, and that all laboratory developed procedures (LDPs) are accurate, precise, clinically relevant, and continually monitored for quality performance. In order to answer stakeholder concerns, and in support of AMP’s dedication to patient care and innovation in the field of molecular pathology, AMP’s experts have prepared and shared with Congress a proposal to modernize the Clinical Laboratory Improvement Amendments (CLIA) program at the Centers for Medicare & Medicaid Services (CMS). The AMP proposal to enhance oversight over laboratory services does not slow innovation or constrain the flexibility and adaptability of LDPs. Most important, it preserves patient access to essential laboratory services provided by academic medical centers, cancer centers, hospitals and health systems, and small independent laboratories that will no longer be offered if a costly FDA-based regulatory system is imposed upon these key health care organizations and the professionals employed by them. FDA has long presented anecdotal information comprised of a short list of LDPs, insisting that the only path forward is FDA oversight. The AMP proposal enhances the current CLIA and raises standards. AMP believes that under its proposal these LDPs can be adequately assessed. Therefore, we urge the Committee to use AMP’s proposal as the basis for legislation that would preserve innovative patient care by building upon the current CMS-based system for oversight of LDPs.

AMP does not believe that the Food and Drug Administration (FDA) is the appropriate agency to regulate LDPs. Our professional members provide medical services. They do not manufacture products. Manufacturing

products for sale and providing a medical service are fundamentally different activities. For this reason and others outlined below, AMP must oppose the proposed Energy and Commerce draft legislation despite the improvements that have been made to the previous draft that the Committee circulated earlier this year.

Although we appreciate the addition of clarifications related to review of modified LDPs and support the requirement that the senior management of any regulatory agency overseeing LDPs include individuals with management experience in clinical laboratory operations, the proposed legislation would not make patients safer. Rather, it would deny seriously ill patients access to necessary, innovative, and potentially lifesaving care at our nation's top academic medical centers and major cancer hospitals.

Moreover, the Committee's draft legislation would interfere with the practice of medicine, and if enacted, threatens to concentrate testing in a few large laboratories that are far removed from patients and ordering physicians, disrupting traditional healthcare teams comprised of pathologists, geneticists, oncologists, and other health care providers. Submitting LDPs for premarket approval by the FDA is financially and administratively unfeasible for most hospital laboratories. The draft legislation also shifts much of product liability from manufacturers to clinical laboratories and medical professionals. These regulatory and legal costs would force laboratories to stop offering a large extent of their services, or close down entirely, resulting in a constriction in patient access to these vital medical services.

AMP's proposal does not address in vitro diagnostic (IVD) test kits; however, we support reform of the regulation of manufactured and distributed IVDs. Current FDA regulations prevent manufacturers from readily modifying, enhancing, or otherwise improving upon commercial kits. This flawed regulatory paradigm limits the choices and options molecular pathologists and other laboratory professionals have as they strive to optimally care for their patients. Still, the provision of LDP services and the design, development, manufacture, packaging, and distribution of IVD kits remain separate and distinct activities with very different underlying medical and economic models, and must continue to be independently regulated.

Unlike manufactured, packaged, and distributed IVD test kits, LDPs are medical services throughout the design, validation, performance, ongoing monitoring, and interpretation of test results. Professional judgment is used during each of these activities, providing continual opportunities to promote test accuracy, reliability and patient safety throughout provision of the services. For an LDP, the defining measure of quality is the direct involvement of an appropriately qualified professional in every aspect of the testing service. This distinguishing feature of all LDPs is not at all incorporated into the Energy and Commerce draft legislation.

The AMP proposal contains a number of salutary features that meet stakeholder concerns. First, AMP addresses adverse event reporting in a manner consistent with the operation of a clinical laboratory rather than a manufactured IVD, utilizing realistic standards based on effects of laboratory test results on patients. Second, AMP's proposal requires that the information be publicly displayed in a searchable, standardized format to enable easy review and comparison among LDPs by treating physicians, laboratories, and patients. The draft legislation does not include a provision of this kind. Finally, in contrast to the Energy and Commerce Committee's proposed legislation, the AMP proposal maintains clinical laboratory oversight under a single agency. The Energy and Commerce legislation would create an overly complex, duplicative regulatory system for LDPs that would place an unreasonable and unmanageable burden on laboratories within academic medical centers, cancer centers, hospitals and health systems, and smaller independent laboratories. For example, the Energy and Commerce draft assigns regulation of "processing" of an LDP to FDA, while placing oversight of performance of and LDP within CLIA. However, it is not clear how processing can be consistently distinguished from performance, or which Agency's rules would govern under specific circumstances. Therefore, we again ask the Committee to use the AMP plan as the basis for any proposed legislation addressing regulation of LDPs to provide the best overall system for patient care.

As an Agency, FDA should continue in the role it knows best, ensuring that the performance characteristics of vendor supplied instruments, test kits, software, and reagents are what manufacturers claim them to be in their labeling, promotional materials, and activities. But the Agency should do so using an approach that is sufficiently flexible to accommodate continual technological developments and exponentially increasing medical and scientific knowledge in a timely manner. In this way, FDA can best contribute to patient welfare and public health, by helping molecular pathologists and other laboratory professionals provide the best care possible to our patients.

AMP has considered the desires of treating physicians and patients and AMP believes that all stakeholders have the same ultimate desired outcome: that laboratory testing procedures be high quality, accurate, and precise. AMP's proposal to enhance CLIA regulations does this while also preserving patient access to testing procedures and ensuring that patients and their treating physicians can work together to determine the best testing and treatment options for each individual. This lies at the heart of precision medicine. AMP's proposal presents a path forward for LDPs used in many contexts including responding to public health emergencies, diagnosing or determining risks of inherited diseases, monitoring disease progression, and informing treatment decisions for patients. The section focused on CLIA within the Committee's draft legislation falls short of what AMP recommends and we urge the committee to use AMP's proposal as the basis for legislation on CLIA modernization.

Thank you again for the opportunity to submit this testimony on this draft legislation. AMP looks forward to working with the Committee and federal agencies to design modernized regulations for LDPs that ensure both analytical and clinical validity as well as provide the nimbleness necessary to foster innovation and enable patient access to appropriate testing. If you have any questions or if AMP can be of further assistance, please contact Mary Williams at mwilliams@amp.org.



UNDERSTAND PREVENT
& CURE CANCER

November 16, 2015

The Honorable Chris Collins
US House of Representatives
1117 Longworth House Office Building
Washington, DC 20515

Dear Congressman Collins:

I am writing to you in anticipation of the Energy & Commerce Committee hearing “Examining the Regulation of Diagnostic Tests and Laboratory Operations” scheduled for Tuesday, November 17, 2015.

As you know, Roswell Park Cancer Institute throughout its 117 year history has been an innovator. Several years ago New York State and Roswell Park made a significant investment into genomics and genetic sequencing at the cancer center creating the Center for Personalized Medicine. The investment was made ahead of the national focus on precision medicine.

The revolution in precision or personalized medicine, which can target the right treatment for a specific and genetically identified disease, is dependent on genetic sequencing. Personalized medicine is completely dependent on the rapid development and use of laboratory developed diagnostic tests (LDTs.) the proposed regulation by the FDA of these tests developed for laboratory use and not for resale could have severe and negative impact on patients and on the type of research done at Roswell Park.

The FDA’s interest in regulating LDTs, as described in their draft guidance, threatens to disrupt care for millions, creating a whole new bureau in the agency for LDTs but offering no appreciable benefit in safety or efficacy.

We appreciate the interest in ensuring that LDTs are safe, effective, and transparent in their value. The Association of Molecular Pathology (AMP) has developed a proposal that in my opinion achieves the right regulatory balance by modernizing the existing federal regulatory schema—the Clinical Laboratory Improvement Amendments administered by CMS and provides a limited role for the FDA when laboratories will not share proprietary methodologies that would allow for validation of their LDTs.

The AMP proposal provides laboratories with the choice of regulatory pathways they will pursue. They can either place their tests in the “clinical commons” and be regulated under CLIA, or maintain proprietary approaches and be regulated under FDA or other authorities that require such information such as the New York State Department of Health.

For the sake of patients and ongoing innovation in cancer research, I urge you to support the AMP proposal as the basis for any bill.

You would be amazed at the work we are doing in genetics here at Roswell Park. The human genome holds the understanding of health and illness. FDA regulation will interfere with our work in achieving this understanding. As a physician, I assure you that FDA regulation of LDTs will reduce access for patients to valuable, even life-saving tests. Another unintended consequence of FDA involvement would be to undermine America's leadership in genetics, diagnostics, research and patient care.

Thank you for considering the AMP proposal as the basis for any legislation regulating LDTs.

Sincerely,

Jan A. Nowak, MD, PhD
Clinical Chief of Molecular Pathology

cc:
The Honorable Fred Upton
Chairman, Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515
Fax: (202) 225-4986

The Honorable Frank Pallone Jr.
Ranking Member, Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515
Fax: (202) 225-9665



November 17, 2015

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
2125 RHOB
Washington, DC 20515

The Honorable Frank Pallone
Ranking Member
Committee on Energy and Commerce
2322A RHOB
Washington, DC 20515

The Honorable Joe Pitts
Chairman
Committee on Energy and Commerce
Subcommittee on Health
2125 RHOB
Washington, DC 20515

The Honorable Gene Green
Ranking Member
Committee on Energy and Commerce
Subcommittee on Health
2322A RHOB
Washington, DC 20515

RE: Laboratory Developed Tests (LDTs) & Proposed Regulatory Oversight Framework - Patient First Focus

Dear Chairman Upton, Ranking Member Pallone, Chairman Pitts and Ranking Member Green:

On behalf of the American Association for Clinical Chemistry (AACC), representing many of the nation's leading laboratory professionals and other diagnostic leaders, I continue to respect and appreciate your leadership and steadfast commitment to patient safety and care within the clinical laboratory medical setting. The topic of laboratory developed tests (LDTs) has received significant attention from policymakers, healthcare professionals, and patients over the last couple of years. AACC remains grateful for your willingness to include and engage our organization throughout this important process.

In response to the increased focus on LDTs, our organization turned to a panel of leading experts on LDT related issues. This group of AACC professionals engaged in thoughtful deliberations to review policy proposals from Congress, the Food & Drug Administration (FDA), and stakeholder groups.

After careful review, AACC remains concerned that some of the current LDT oversight proposals may result in negative consequences for patients and the clinical healthcare teams and medical institutions that rely on accurate and timely laboratory results to make critical, immediate, and frequently lifesaving decisions in the course of patient care.

Specifically, our clinical laboratory professionals remain concerned that without further refinement, the present legislative proposal before this House Committee will:

- Foster an anti-competitive environment;
- Stifle test innovation; and
- Hinder patient care.

AACC has long supported federal oversight of LDTs. These tests are currently regulated by the Centers for Medicare and Medicaid Services (CMS) and its deemed private accrediting organizations under the Clinical Laboratory Improvement Amendments (CLIA). We are concerned that substantive, costly changes are being proposed despite the lack of evidence that current processes are insufficient. Further, under the draft legislation, the FDA—which has no experience regulating laboratory practices—would supplant CMS as the federal agency overseeing laboratory developed tests.

Based on AACC's most recent review of the draft LDT legislation under consideration by the House Energy & Commerce Subcommittee on Health, our organization submits for your consideration the following patient-focused policy recommendations:

Comments on Draft Legislation

- AACC supports the use of a risk-based approach for stratifying LDTs and determining the appropriate level of oversight.
- We agree that modifications to an FDA cleared or approved test kit should not automatically result in additional regulatory oversight.
- Certain categories of tests, such as newborn screening and testing for unmet needs and public emergency testing, do not require greater regulatory scrutiny.
- Laboratories should demonstrate analytical and clinical validity for the LDTs they perform.
- The draft LDT legislation would grant complete authority to the FDA for overseeing the development, introduction and validation of LDTs, including assessing the analytical validity of a test—a current responsibility of CMS. In addition, any modification of LDTs would need to be reported to the agency, in many cases subject to prior approval.
- The legislative proposal would grant the FDA powers to inspect laboratories and force them to meet new post-market reporting requirements that essentially redefine hospitals, commercial laboratories, and physician office laboratories performing LDTs as medical device manufacturers.

- AACC is concerned that a new dual regulatory structure for laboratories performing LDTs as defined in the draft legislation will stifle test innovation, particularly developing areas of testing such as those used in precision medicine, and force many hospitals and rural testing facilities to stop performing LDTs, thus impeding patient access to testing.
- Most clinical laboratories cannot afford the additional regulatory and financial costs associated with this draft legislation. As proposed, the current legislative draft could result in an anti-competitive system that favors the few laboratories with sufficient resources to comply with FDA requirements that were developed for manufacturers, thereby creating a situation wherein testing costs could rise.
- Our interpretation of the draft bill is that it will eliminate the 510(k) clearance and pre-market approval processes for tests developed and marketed by in vitro diagnostic (IVD) manufacturers. This proposal would be a significant change from the current review process. While AACC agrees that Congress should perhaps explore reforms to this area, this manufacturing issue is entirely separate from the regulation of tests developed and performed in individual clinical laboratories. Any change in the IVD company submission process should be considered separately from LDT oversight.
- Whereas the FDA clears and approves test kits to be used in a variety of medical settings by a diverse group of health care personnel, LDTs can only be developed and performed by high complexity CLIA laboratories under the direction of highly trained and experienced personnel. Although each is invaluable to patient care, LDTs and IVD medical devices are distinctly different tools in the health care process and as such they need to be discussed and regulated differently.

Use of Existing Regulatory Structure

AACC recommends that Congress utilize the existing CLIA regulatory framework to address concerns regarding LDT oversight. These established standards can be easily adapted, eliminating the need for new regulatory mechanisms. What follows is a limited list of suggested policy changes that could be accomplished through the existing regulatory model.

Notification and Listing of LDTs

The draft legislation would require that laboratories performing LDTs notify the FDA that they are performing such tests and provide a listing of the tests. CMS would be the more logical, readily available repository for this information and already has in place a mechanism for addressing the issue. All CLIA laboratories must submit a laboratory activity list to the agency that includes all the tests it performs, including LDTs, as well as the methodologies utilized.

The College of American Pathologists (CAP), a key private accrediting body, requires that laboratories provide a specific list of all LDTs they perform. Any additional information could be gathered under the current regulatory framework.

Validation of LDTs

AACC agrees that clinical laboratories using LDTs should demonstrate the analytical and clinical validity of the test prior to its use. Updates or modifications to the validation process should take place within the CLIA framework.

CLIA requires laboratories performing LDTs to document the analytical validity of the test. Most laboratories utilizing LDTs voluntarily obtain accreditation from more rigorous CLIA accrediting organizations, such as CAP and the Joint Commission, that require laboratories to also demonstrate the clinical validity of LDTs.

Classification and Prioritization of LDTs

AACC supports a risk-based classification approach for determining the level of oversight for LDTs. This regulatory scheme should include three categories: high, moderate, and low risk.

Moderate and low risk LDTs—which would represent the vast majority of such tests—should remain exclusively under CLIA.

Tests in the high-risk category—for example LDTs for which significant proprietary information limits the ability to independently verify the accuracy of the test, and direct-to-consumer tests for which the absence of professional consultation/interpretation could lead to serious patient harm—should be jointly regulated by FDA and CMS.

Reporting Testing Errors

Clinical laboratories work diligently to provide laboratory test results that meet the customer expectations the great majority of the time. When a laboratory identifies that a testing error has occurred, it should report that mistake to the appropriate oversight body.

According to a scheme in which high-risk tests are under dual regulation, adverse events involving these tests would be reported to the FDA and CMS. Errors involving low and moderate risk tests would remain under the current CLIA reporting structure, which requires laboratories to document and report the errors to CMS and the appropriate accrediting bodies, the organization's risk management department, and the physician.

Summary

AACC believes the current regulatory structure can be modified to address concerns regarding LDTs, without introducing costly, burdensome dual oversight for which there is neither evidence of need nor proof of improvement over the current system. The vast majority of LDTs should remain under direct CMS oversight with a small number of high-risk tests jointly overseen by both CMS and FDA. We are concerned that the current draft legislation will greatly restrict the ability of clinical laboratories to develop and provide the tests needed to care for their patients, will diminish the number of laboratories with the resources to do so, and significantly hinder patient care and access to testing.

AACC is a global scientific and medical professional organization dedicated to clinical laboratory science and its application to healthcare. AACC brings together more than 50,000 clinical laboratory professionals, physicians, research scientists, and business leaders from around the world focused on clinical chemistry, molecular diagnostics, mass spectrometry, translational medicine, lab management, and other areas of progressing laboratory science. Since 1948, AACC has worked to advance the common interests of the field, providing programs that advance scientific collaboration, knowledge, expertise, and innovation.

On behalf of AACC, I would like to thank you for the opportunity to provide comments to the subcommittee on this most important issue. If you have any questions, please do not hesitate to contact me directly at ddkoch@emory.edu or Vince Stine, PhD, Director of Government Affairs, at vstine@aacc.org.

Sincerely,

A black rectangular box redacting the signature of David D. Koch.

David D. Koch, PhD, DABCC
President, AACC

FRED UPTON, MICHIGAN
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FOURTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115
Majority (202) 225-2927
Minority (202) 225-3841

December 7, 2015

Dr. Jeffrey Shuren
Director
Center for Devices and Radiological Health
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Shuren:

Thank you for appearing before the Subcommittee on Health on November 17, 2015, to testify at the hearing entitled "Examining the Regulation of Diagnostic Tests and Laboratory Operations."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on December 21, 2015. Your responses should be mailed to Graham Pittman, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to graham.pittman@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

FRED UPTON, MICHIGAN
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
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Minority (202) 225-3841

December 7, 2015

Dr. Patrick Conway
Deputy Administrator for Innovation and Quality
Chief Medical Officer
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Dear Dr. Conway:

Thank you for appearing before the Subcommittee on Health on November 17, 2015, to testify at the hearing entitled "Examining the Regulation of Diagnostic Tests and Laboratory Operations."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

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Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

Patrick Conway's Hearing
 "CLIA"
 Before
 E&C Health Subcommittee
 November 17, 2015

Attachment — Additional Questions for the Record

The Honorable Marsha Blackburn

1. **Dr. Conway, rather than having an either/or approach to testing oversight, might there be another option?**

Answer: We agree that oversight of laboratory testing need not take an either/or approach in terms of CMS' responsibilities versus those of other agencies. In fact, we believe the most effective approach is to build on the collaborative inter-agency approach that is in effect today. CMS, the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) all work together to assure accuracy and reliability of laboratory testing under CLIA, supplementing FDA's separate responsibility for assuring the safety and effectiveness of laboratory tests. These multi-agency efforts are different in focus, scope, and purpose, but they build on the strengths of each agency and are complementary. The division of labor in administering CLIA was carefully designed to ensure that each agency is using its expertise and infrastructure in a way that is not duplicative.

When CLIA was implemented in the early 1990s, the responsibility for certification of laboratories was a natural fit for CMS because of our survey and certification experience. Other CLIA activities, like the categorization of tests, are better suited to the FDA, which in addition to its CLIA role, is positioned to assess clinical validity, conduct premarket reviews, and perform other necessary oversight activities primarily under the Federal Food, Drug, and Cosmetic Act.

CMS is committed to ensuring high quality, accurate, and reliable laboratory testing by assuring that laboratories have appropriate controls, expertise, training, and procedures. We believe CLIA and our implementing regulations create the necessary framework to effectively oversee laboratories' day-to-day operations today and into the future (including those operations that pertain to laboratory-developed tests).

2. **The American College of Medical Genetics and Genomics has proposed a risk-based oversight system for regulation of genetic Laboratory Developed Tests which entails CLIA enhancement and uses a third-party review system for tests being offered. Since the majority of the work requiring scientific and medical genetic expertise would be performed by 3rd parties, if CMS were to implement such a model, how many additional FTE's would CMS/CLIA need?**

Answer: CMS shares your interest in ensuring that all laboratory-developed tests (LDTs) – including those LDTs using genetic and genomic technology – provide accurate and clinically-relevant results to patients and providers. However, any estimate of resources needed to implement the American College of Medical Genetics and Genomics’ proposal would be premature at this time. We are not familiar with the details of the proposal, which could affect agency resources; nor is it possible to estimate the volume of tests that might be involved, how new third-party reviewers would be selected and monitored, and any other new responsibilities that CMS would be required to assume.

We also note potential concerns about proposals that would change the current collaborative framework of responsibilities in laboratory oversight (including for LDTs), which is carefully designed to balance the strengths of each partner agency. For example, the FDA has the expertise and infrastructure to conduct pre-market assessments of LDTs for safety and effectiveness, including clinical validity. In contrast, CMS is responsible for certifying and surveying laboratories under CLIA and has long-standing survey and certification experience.

The Honorable Michael C. Burgess

1. In a June 2006 GAO Report, the GAO indicated that the CLIA program “had a carryover balance of \$70 million” as of September 30, 2005. Please detail for the Committee the current funding status of the CLIA program, including a breakdown of revenues (i.e. user fees or other appropriations) and outlays (i.e. detailing administrative outlays, salary outlays, and those outlays attributable to inspection activities, or other) in 2014, and whether the CLIA program still maintains a carryover balance.

Answer:

A. Cash Balance: As a result of careful stewardship of CLIA funds, together with consistency in the workload, CMS has consistently maintained a cash balance in the CLIA user fee fund. This has enabled CMS to avoid any fee increase for laboratories under CLIA for more than 16 years.

However, in recent years, the total revenue received each year has not fully paid for the total CLIA costs, thus reducing the cash balance in the CLIA user fee fund.

The most recent annual financial gap ranges from \$5.9 million in FY2014 to \$10 million in FY2016.

As a result of the growing gap in revenues versus expenses, the CLIA cash balance that is carried over from one year to the next is gradually declining from \$55.6 million in FY2015 to \$45.6 million in FY2016.

Year	Revenues	Outlays	Net Annual	Balance
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FY2013				\$68.2
FY2014	\$54.0	\$59.9	(\$5.9)	\$62.3
FY2015	\$53.7	\$60.3	(\$6.7)	\$55.6
FY2016	\$52.1	\$62.1	(\$10.0)	\$45.6

B. Types of Expenses: CLIA is administered through a collaboration of three federal agencies (CMS, FDA and CDC) and State Survey Agencies (SAs).

The State SAs and other contractors perform most of the onsite surveys and complaint investigations of laboratories that hold a certificate of compliance or certificate of registration, as well as validation surveys that check on the adequacy of surveys conducted by CMS-approved accrediting organizations for laboratories that hold a certificate of accreditation.

CMS maintains the CLIA regulations and policies, and monitors the work carried out by State SAs' surveyors, as well as carrying out enforcement actions when State SA or other contractor surveys identify deficiencies in laboratory compliance with CLIA regulations.

The FDA administers the classification system by which tests are categorized as waived, moderate, or high complexity tests. CLIA requirements are calibrated to the degree of complexity involved in each type of test. The FDA may also perform premarket review, and analyze clinical validity and analytic validity of tests, but does so primarily under the Federal Food, Drug, and Cosmetic Act.

The CDC conducts research, staffs the Secretary's Clinical Laboratory Improvement Advisory Committee, and other functions. Below is the FY2016 budget for each agency. The table below does not include the 6.8% sequestration reduction.

Major Category of Expense (millions)	FY2016
Costs - State Survey (Inspections)	\$19.29
Costs - CDC	\$11.73
Costs - FDA	\$4.09
Costs - CMS	\$23.55
TOTAL	\$58.66

C. Administrative Expenses. The table below shows CMS' administrative expenses, excluding costs of the State-conducted onsite surveys. The expenses encompass both CMS central and regional office expenses, contracts, agency overhead, the information systems and databases through which all State and CMS surveys are documented and maintained, the CLIA regulations and policies, monitoring the work carried out by State SAs' surveyors, as well as carrying out enforcement actions when State SA or other contractor surveys identify deficiencies in laboratory compliance with CLIA regulations.

CMS Administrative & Oversight Expenses (millions)	FY2016
Salaries	\$9.89
Overhead	\$7.45
CLIA Data System Contract	\$2.67
Other- Specialty Inspection Contracts	\$0.80
Cytology- Specialty Inspection Contract	\$1.55
Administrative-Other	\$1.19
TOTAL	\$23.55

2. Regarding CMS-conducted laboratory inspections under CLIA, please provide the following:
- a. The primary inspection objectives for an inspector;
 - b. The number of CMS laboratory inspections conducted per year (not including those inspections conducted by deemed organizations); and
 - c. The number of inspection findings by CMS per year that the agency would deem as “serious,” that “create a probability of risk to patients,” or that warrant the sanctioning or closure of a CLIA laboratory. Additionally provide a categorical breakdown of the types of such findings.

Answer:

- a. The primary objectives for a laboratory surveyor (the CLIA program’s term for an inspector) are described in Appendix C of the State Operations Manual. They include determining the laboratory’s compliance with CLIA requirements, and assisting laboratories in improving patient care by emphasizing aspects of the regulatory provisions that have a direct impact on the laboratory’s overall performance. CMS promotes the use of an educational survey process, especially on initial laboratory inspection, to help laboratories understand and achieve the minimum quality standards established by CLIA. The surveyor is responsible for assessing the laboratory’s performance based on review of the laboratory’s past and current practices, interviews with the laboratory’s personnel, and review of the laboratory’s records. CLIA surveyors meet these objectives by employing an outcome-oriented approach focused on the overall performance of the laboratory and the way it monitors itself, rather than a methodical evaluation of each regulatory requirement (apart from “condition-level” deficiencies, discussed further below).
- b. Each year, CMS conducts initial surveys of laboratories seeking a CLIA Certificate of Compliance (CoC), which are resurveyed every 2 years for recertification purposes. CMS also conducts validation surveys in a sample of laboratories deemed to meet CLIA requirements through accreditation by an approved private accrediting organization. Laboratories that only perform tests categorized as waived obtain a CLIA Certificate of Waiver (CoW), and are not subject to the CLIA nonwaived testing requirements, such as mandatory on-site surveys every two years. Laboratories holding a CoW may receive voluntary surveys (conducted in conjunction with the CDC). Additional surveys may be initiated based on complaints from the public, or unsuccessful proficiency testing by the laboratory. Finally, surveys of laboratories performing cytology testing are conducted by a specialized CMS contractor.

Table 1, below, shows the average number of surveys conducted each year, in each category, from fiscal year (FY) 2011 through FY 2015 (not including surveys conducted by private accrediting organizations):

Table 1: Surveys Conducted (FY 2011–FY 2015)

Survey Type	Average annual number performed
Initial surveys of CoC laboratories	1,221
Recertification surveys of CoC laboratories	8,244
Validation surveys	356
Certificate of Waiver voluntary surveys	1,975
Complaint surveys	178
Unsuccessful proficiency testing surveys	2,548
Specialized cytology surveys	47

- c. When a CLIA survey identifies a deficient practice in a laboratory, the surveyor cites the appropriate requirement in the CLIA regulations with which the laboratory is non-compliant. A “condition-level” deficiency is more serious than a “standard-level” deficiency, and must be corrected for the laboratory to continue patient testing. If sufficient correction is not demonstrated, CMS may initiate enforcement actions that could lead to termination of the laboratory’s CLIA certificate (without which it may not operate). Table 2, below, shows the top 10 condition-level deficiencies cited nationally, based on survey data for 17,389 laboratories holding a Certificate of Compliance (CoC) as of December 2015. The survey data reflect surveys that occurred in FY2014 and FY2015 since laboratories are on a two-year survey cycle. The data represent the number of laboratories cited for each condition-level deficiency, and one or more conditions may be cited for each laboratory. For example, 555 CoC laboratories were cited for the first condition-level deficiency (Requirements for Moderate Complexity Laboratory Director) listed in Table 2. Some of those same laboratories may also have been cited for one or more of the other condition-level deficiencies listed in this table.

Table 2: Top 10 Condition-level Deficiencies (FY2014 & FY2015)

Condition Cited	Total Number of Labs Cited Nationally	Percentage (%) of National Total*
Requirements for Moderate Complexity Laboratory Director	555	3.2
Requirements for Successful Proficiency Testing (PT) Participation	375	2.2
Requirements for High Complexity Laboratory Director	262	1.5
Monitoring of Analytic Systems	236	1.4
Requirements for PT Enrollment and Testing of PT Samples	220	1.3
Requirements for Technical Consultant – Moderate Complexity	165	0.9
Requirements for Laboratory Personnel – Moderate Complexity	160	0.9
Hematology Quality Control	92	0.5

Requirements for Testing Personnel – High Complexity	90	0.5
Requirements for Technical Supervisor – High Complexity	61	0.4

*This column represents the percentage of the labs cited for each of the top 10 identified condition-level deficiencies cited nationally out of the total number of CoC laboratories (17,368) surveyed during one survey cycle in FY 2014 & FY2015).

The CLIA statute contains special rules for cytology testing including workload limits, specialized proficiency testing and personnel standards, and quality control procedures, reflecting Congress' particular concern about such testing when CLIA was enacted in 1988. Laboratories that perform cytology tests are surveyed by a specialized CMS contractor, which selects a sample of these laboratories to survey each year. An average of 47 specialized cytology surveys were conducted each year from FY 2010 through FY 2014. During that period, 37.3% of the cytology laboratories surveyed were cited for condition-level deficiencies. Table 3, below, shows the top 5 condition-level deficiencies cited at cytology laboratories surveyed by the CMS contractor for FY 2010 through FY 2014.

Table 3: Condition-level Deficiencies in Cytology Laboratories (FY 2010-FY 2014)

Condition Cited	Total Number of Times Cited Nationally
Requirements for High Complexity Laboratory Director	66
Requirements for specialty of Cytology	40
Requirements for Technical Supervisor – High Complexity	27
Requirements for Proficiency Testing (PT) Enrollment and Testing of PT Samples	14
Requirements for Successful PT Participation	9

3. Dr. Conway's written statement indicates that "CMS does not have a scientific staff capable of determining whether a test is difficult to successfully carry out or likely to prove detrimental to a patient if carried out improperly." However, as CMS acknowledges on CMS.gov, "the objective of the CLIA program is to ensure quality laboratory testing." How does CMS accomplish this mission without the ability to determine whether a test is difficult to carry out or likely to harm a patient?

Answer: As noted, CMS is responsible, under CLIA, for oversight of laboratories' day-to-day operations and procedures, including qualifications, training and proficiency of their personnel, performance assessments of their equipment, proper handling of specimens, etc.

This function is distinct from assuring the safety and effectiveness of laboratory tests, and does not include premarket review of laboratory tests, for which the FDA has the necessary authority (primarily under the Federal Food, Drug, and Cosmetic Act), and expertise.

FDA is also a critical partner in administering CLIA, which created a system of laboratory oversight based on test complexity. FDA's primary responsibility under CLIA is to classify clinical laboratory tests into one of three categories (waived, moderate complexity, and high complexity) based on their level of complexity and risk to patients if performed incorrectly. All tests introduced in the United States are considered high complexity by default unless FDA categorizes a test as waived or moderate complexity. FDA does not categorize tests that are designed, manufactured, and used within a single laboratory, known as laboratory-developed tests (LDTs). Thus, by default, they are considered to be high complexity tests.

Standards that laboratories must meet under CLIA are based on the complexity of tests they perform. Laboratories that perform more complex tests must meet higher standards. Laboratories that perform moderate and high complexity tests must meet requirements for quality assessment, quality control, personnel qualifications and education, general laboratory systems, and proficiency testing, among others. Laboratories that perform only waived tests – which are cleared by FDA for home use, or are simple and accurate with negligible risk of an erroneous result and pose a low risk to patients if performed incorrectly – are exempt from most CLIA requirements.

CMS enforces CLIA standards by requiring laboratories to obtain a certificate in order to operate, and conducting on-site surveys. Laboratories performing the same test must meet the same standards, whether located in a hospital, doctor's office or other site. CLIA's provisions apply to all laboratories in the United States, not just those that receive Medicare payment, in order to ensure uniform quality across all laboratories.

4. During the hearing, Dr. Conway indicated that seven organizations are currently deemed authorities under CLIA. Please provide the following:

- a. The names of each of the deemed authorities;
- b. The number of inspectors fielded by each organization as compared to CMS;
- c. The types of expertise and qualifications of the inspectors of each organization as compared to inspectors fielded by CMS;
- d. The number of laboratory inspections per year, per organization as compared to CMS; and
- e. A description of how inspections by a deemed organization may differ from an inspection conducted by CMS.

Answer: The following table presents information on each of the seven accrediting organizations currently approved by CMS under CLIA. This information was provided by the accrediting organizations; thus we note that not all information is described consistently across entities, and may represent different time periods. The last column shows comparison information for surveys conducted by CMS or its contractors.

	A2LA	AABB	AOA/HFAP	ASHI	CAP	COLA	T
Organization Name	American Association for Laboratory Accreditation	Formerly known as the American Association of Blood Banks	American Osteopathic Association/Healthcare Facilities Accreditation Program	American Society for Histocompatibility and Immunogenetics	College of American Pathologists	Formerly known as Commission on Laboratory Accreditation	Th
Number of Inspectors	19	5 AABB employees (team leaders), and approx. 700 volunteer inspectors	16	150	25 CAP employees (staff inspectors and techs), and about 9,700 volunteer inspectors	24	Cc
Inspector Expertise/Qualifications (as described by each organization)	Bachelor's degree, 10 years experience.	Bachelor's degree in medical technology or related discipline, 3 years experience, in-depth knowledge of specialty areas. Training to maintain their competency to inspect.	At least a Bachelor's degree with certification as a medical technologist by the American Society for Clinical Pathology.	Employed at ASHI-accredited laboratories and familiar with all tests of each laboratory they inspect.	Practicing laboratorians trained to do inspections. Includes pathologists, Ph.Ds, medical technologists, respiratory therapists, histotechs, geneticists.	10-30 years experience. Ongoing training. Subject matter experts hired as needed.	M/ Te w/ de. rel dis Pr lic rec lav wi na ac or ex or tec sp set mu at of me ex
Laboratories Inspected each	2 ¹	100	90	100	4,000	4,000	

¹ A2LA is a recently approved accreditor; thus they had completed considerably fewer surveys than the other accreditors at the time this information was reported.

	A2LA	AABB	AOA/HFAP	ASHI	CAP	COLA	T
year							
Description of Inspections	Consists of defined steps for inspector preparation and on-site inspection.	An in-depth audit of the quality management system and technical requirements as specified in AABB Standards; also incorporates CLIA requirements. The quality system approach is a holistic review of an organization's policies, processes and procedures.	Material reviewed during a survey/ inspection covers all CLIA regulations.	More in-depth review of HLA typing in the laboratory (identifying an individual's unique pattern of HLA antigens); some standards are more stringent than CLIA.	A team of experts from disciplines of the tests performed in the laboratory uses 21 discipline-specific checklists, including focus on emerging technologies. Instructions suggest open-ended questions, specific documents to sample, tracers to follow, and practices to observe.	Based on CLIA standards plus additional standards. Laboratories with serious or systemic noncompliance are referred to a special technical team that determines additional requirements and next steps.	Su is pa ce ev un sy an op usi ap Su tra me rec su "tr ex a p thr org

5. CMS materials indicate that the States of New York and Washington have “CMS approved laboratory program(s).” Please provide the following:
- Describe the difference in these state laboratory programs from those under CLIA.
 - Further, the Committee understands New York State also inspects laboratories that are not located in New York State but provide services on patient samples originating in New York. How do these inspections and policies differ and intersect with CMS CLIA operations?

Answer: Washington and New York have CMS-approved state laboratory licensure programs equal to or more stringent than the CLIA program. While laboratories in these states must register with CMS for a CLIA identification number, these state programs have oversight authority for the laboratories located in their respective states.

a. Washington’s survey and enforcement process is substantially equivalent to the CLIA process, but includes the following requirements that are different or more stringent than CLIA:

- Washington’s enforcement process in regard to proficiency testing (PT) requirements is stricter than CLIA.
- Washington offers new state-inspected laboratories a free technical assistance visit, prior to their first inspection.
- All cited deficiencies must be corrected within 60 days of acceptance of the plan of correction. If the laboratory has repeat deficiencies from its previous 2 surveys, it gets a 1 year on-site follow-up survey for which it is billed. In contrast, CLIA has different timeframes for correction of deficiencies based on severity of the deficiency. Condition-level deficiencies must be corrected within 90 days and standard-level deficiencies must be corrected within 12 months. Repeat deficiencies are evaluated to determine if the level of overall noncompliance should be increased, which may affect enforcement actions.
- Washington surveyors assess whether clinical validity of a laboratory-developed test (LDT) has been established. If the laboratory has no evidence that clinical validity has been established, the surveyor may ask that a disclaimer be placed on the report, stating that the test has not been clinically validated. CLIA surveyors do not evaluate the clinical validity of LDTs, as clinical validity falls under the scope of the FDA, not CMS,

New York State’s (NYS) Public Health Law is broader than CLIA in how it defines a “clinical laboratory.” For example, NYS regulates forensic identity testing, parentage identity testing, forensic toxicology testing, and tests on some alternative types of samples. Laboratories that perform only the technical component of histopathology testing are also required to obtain a permit. These types of activities are not covered by CLIA. In addition, if a laboratory performs steps in the testing process at multiple locations – for example, processing of the specimen is performed at one location, testing/analysis at another location, interpretation at a third location, and reporting of

results at a fourth location -- each location must obtain a NYS permit. CLIA does not require a certificate for facilities that only perform specimen processing. In addition:

- The NYS law authorizes State experts to review LDTs to determine whether the proposed testing is both analytically and clinically valid, before the testing can be performed on specimens from NYS. CLIA does not address clinical validity.
- A laboratory may not perform testing either in NYS or on specimens from NYS until it has met on-site survey, proficiency testing, and validation requirements, if applicable, and has been issued a NYS permit. In contrast, CLIA allows laboratories to begin testing with a Certificate of Registration prior to the initial survey, which is performed 3-12 months after testing as begun.
- The NYS law defines specific training and education requirements for laboratory directors, which are more stringent than CLIA. For example, the director must have relevant training/experience obtained within the last 6 years to direct testing in a specific specialty/category.
- Some NYS specialty standards, such as for genetic testing, require that all reports be signed by the qualified person who reviewed, approved, and interpreted the test results. In general, CLIA is less prescriptive.
- The NYS law defines a supervisor as a licensed clinical laboratory technologist with 6 years of post-licensure clinical experience. In contrast, CLIA requirements for technical supervisors differ by educational level. The longest period required by CLIA is for Bachelor's degree-level applicants, who must have 4 years of experience in the specialty/subspecialty they are supervising.

b. In regard to testing performed on patient specimens originating in New York State, the NYS law does not differentiate between laboratories located in NYS and those serving New York residents that are located outside of NYS. Thus, all laboratories performing testing in NYS, or on NYS samples, must meet State requirements to be eligible for a NYS permit. Similarly, since CLIA applies to all laboratories in the U.S., inspections and policies under CLIA are not based on location of the laboratory.

6. On April 16, 2015, the FDA and CMS announced the formation of the "Task Force on LDT Quality Requirements." Please provide the following:

- a. The scope of the Task Force's work;
- b. When findings or conclusions of the Task Force will be made public and, if not to be made public, the rationale for not making public;
- c. The anticipated time period the Task Force is expected to operate; and
- d. The extent to which the Task Force is coordinating with industry, and/or provider, and/or patient stakeholders.

Answer: To coordinate efforts across the Department of Health and Human Services, FDA and CMS established an interagency task force in April 2015 to continue and expand on our collaboration related to the oversight of laboratory-developed tests (LDTs). The Task Force, comprised of leaders and subject matter experts from each agency as well as NIH and CDC, is working to address a range of issues, including those involving quality requirements for

LDTs. There is no set endpoint for the Task Force, which will continue operating as long as it is determined to be useful by the participating agencies.

The Task Force goals include:

- Clarifying FDA and CMS roles in the oversight of LDTs and clinical laboratories.
- Addressing the needs and concerns of clinical laboratories in regard to their development of LDTs, and how laboratories would implement the FDA Quality System regulation requirements.
- Investigating how to best leverage joint resources to develop appropriate training, avoid duplication, and maximize efficiency of efforts.

The first product of the Task Force was a joint blog, detailing FDA and CMS responsibilities with regard to LDTs and clinical laboratories. The blog was published on both FDA and CMS CLIA websites on April 17, 2015. FDA also held meetings with each of the CLIA-approved accreditation organizations to review their survey processes.

The Task Force will also seek and facilitate input from a range of stakeholders including industry, providers, and patient advocates, through public forums and other information-sharing processes.

Underlying the Task Force's work is FDA's and CMS' agreement on their complementary roles in regulating laboratories and laboratory tests. CMS, under CLIA, focuses on the laboratories' overall performance whereas FDA, under the Federal Food, Drug, and Cosmetic Act (FFDCA), focuses on the safety and effectiveness of LDTs. Although each agency's role is different, FDA and CMS share an interest in ensuring effective and efficient oversight of LDTs so laboratories can offer innovative tests to the American public with confidence that they are accurate and provide clinically meaningful information, without unnecessary or duplicative agency oversight.

The Honorable Frank Pallone, Jr.

The Clinical Laboratory Improvement Amendments are quality standards that apply to all clinical laboratories to ensure that test results are accurate and reliable. The standards a lab must meet correspond with the complexity of the test – labs performing more complex tests must meet higher standards – and are focused on personnel qualifications, laboratory systems, quality control and proficiency testing. Some stakeholders have advocated for a modernized CLIA as a way to address gaps in oversight over LDTs.

To better understand the limitations of CLIA's authority in comparison to the FDA's proposed regulatory framework, please respond to the following questions:

- 1. Does CMS require labs to provide any evidence that the tests labs are performing are producing accurate results?**

Answer: CMS looks for evidence of test analytical accuracy during the on-site surveys. CLIA requires the laboratory to have documented evidence of analytical validation, proficiency testing, quality control, quality assessment monitors, etc.

2. Does CMS require labs to provide evidence that would support claims they make about their tests?

Answer: CLIA does not address clinical claims about tests made by a laboratory.

3. Does CMS collect or report on any adverse events for tests?

Answer: No, CMS does not collect or report on any adverse events related to testing devices. We report on laboratories on which sanctions have been imposed related to risk of patient harm due to deficiencies in laboratory operations.